Tetrahedron 69 (2013) 8798–8808

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot synthesis of 1-substituted-5-alkylselanyl-1*H*-tetrazoles from isoselenocyanates: unexpected formation of *N*-alkyl-*N*-arylcyanamides and (*Z*)-*Se*-alkyl-*N*-cyano-*N*,*N*′-diarylisoselenoureas

Galina Karabanovich [a], Jaroslav Roh [a,*], Zdeňka Padělková [b], Zdeněk Novák [a], Kateřina Vávrová [a], Alexandr Hrabálek [a]

[a] Department of Inorganic and Organic Chemistry, Faculty of Pharmacy in Hradec Králové, Charles University in Prague, Heyrovského 1203, Hradec Králové 50005, Czech Republic
[b] Department of General and Inorganic Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentská 573, Pardubice 532 10, Czech Republic

ARTICLE INFO

Article history:
Received 15 April 2013
Received in revised form 11 July 2013
Accepted 22 July 2013
Available online 4 August 2013

Keywords:
Selenium
Isoselenocyanate
Tetrazole
Cyanamide
Tetrazole-5-selenol

ABSTRACT

1-Substituted-5-alkylsulfanyl-1*H*-tetrazoles are well known class of organic substances with various applications in medicinal chemistry or photographic industry. Their selenium analogues, 1-substituted-5-alkylselanyl-1*H*-tetrazoles are, however, much less explored because of the lack of suitable methods for their preparation. In this work we investigated the synthesis of 1-alkyl/aryl-5-alkylselanyl-1*H*-tetrazoles from synthetically available alkyl/arylisoselenocyanates. One-pot reactions of arylisoseleno cyanates with sodium azide and alkylating agent led to the target 5-alkylselanyl-1-aryl-1*H*-tetrazoles but also to interesting side products, namely *N*-alkyl-*N*-arylcyanamides and (*Z*)-*Se*-alkyl-*N*-cyano-*N*,*N*′-diarylisoselenoureas. Nevertheless, when alkylisoselenocyanates were utilized as the substrates, the reactions led exclusively to the formation of 1-alkyl-5-alkylselanyl-1*H*-tetrazoles in good yields. This simple one-pot procedure brings new possibilities for the preparation of variously substituted selenium compounds. It also opens the way to further investigations of selenium isosteres of the widely utilized 5-thiotetrazole moiety in biomedical applications.

1. Introduction

Selenium is a trace element, essential for normal human development, growth, metabolism, and function of the immune system. Originally, selenium was considered as one of the most toxic elements. Its benefits were not fully appreciated until 1957, when Schwarz and Foltz described the relationship between selenium intake by food and prevention of liver necrosis in rats.[1] In 1973 it was discovered that selenium is a part of glutathione peroxidases $GSHP_x$, antioxidant proteins that reduce potentially damaging reactive oxygen species, such as hydrogen peroxide and lipid hydroperoxides, to harmless products.[2] In recent years increasing attention has been paid to selenium-containing compounds due to their use as synthetic tools,[3] and as promising biologically active substances exhibiting antifungal,[4] antimycobacterial,[5] antiviral,[6] antitumor[7] or antihypertensive properties.[8]

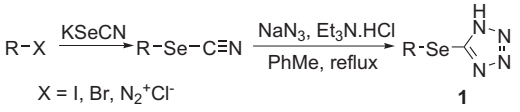
Our group has been interested in the chemistry of tetrazole-containing compounds, especially 5-substituted tetrazoles and substituted tetrazole-5-thiols. Tetrazoles are a well-described class of nitrogen-containing heterocycles with valuable properties, which have found widespread application in various fields of industry and science, mainly in medicinal chemistry as lipophilic and metabolically stable surrogates for other functional groups.[9,10] Tetrazole-5-thiols are also a frequent fragment of pharmaceutically active compounds. The best-known examples of drug containing 1-substituted-5-alkyl/arylsulfanyl-1*H*-tetrazole are the β-lactam antibiotics of the cephalosporin and cephamycin series, which exhibit low toxicity and a wide spectrum of antibacterial activity.[10] In addition, 1-aryltetrazol-5-ylthioacetanilides were identified as potent inhibitors of HIV-1RT with low nanomolar intrinsic activity on the enzyme and submicromolar antiviral activity in HIV infected cells.[11] In a series of 1-substituted 5-alkyl/arylsulfanyl-1*H*-tetrazole compounds, antitubercular,[12,13] antibacterial,[14] and antifungal activities[15] were found.

Although the chemistry of selenium compounds is quite similar to the chemistry of sulfur compounds, 1-substituted-5-alkyl/arylselanyl-1*H*-tetrazoles have been much less explored compared to

* Corresponding author. Tel.: +420 495067339; fax: +420 495067166; e-mail addresses: jaroslav.roh@faf.cuni.cz, roh_j1aa@faf.cuni.cz (J. Roh).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.07.103

their sulfur isosteres. Most publications dealing with 5-selanyl tetrazoles describe the syntheses of 5-alkyl/arylselanyl-1*H*-tetrazoles (**1**) based on the reaction of alkyl/arylselenocyanates with sodium azide under various conditions (Scheme 1).[16–18] 5-Alkyl/arylselanyl-1*H*-tetrazoles could be subsequently functionalized. However, low regioselectivity of these reactions leads to the formation of 1,5- and mainly 2,5-disubstituted derivatives.[9,19] A series of compounds **2** (Fig. 1), which have been synthesized from corresponding 5-arylselanyl-1*H*-tetrazoles and *p*-toluensulfonic acid using dicyclohexylcarbodiimide, can be shown as an example.[20] However, the resulting 1,5-regioisomer was not fully confirmed.



Scheme 1. Synthesis of 5-alkyl/arylselanyl-1*H*-tetrazoles from alkyl/arylselenocyanates.

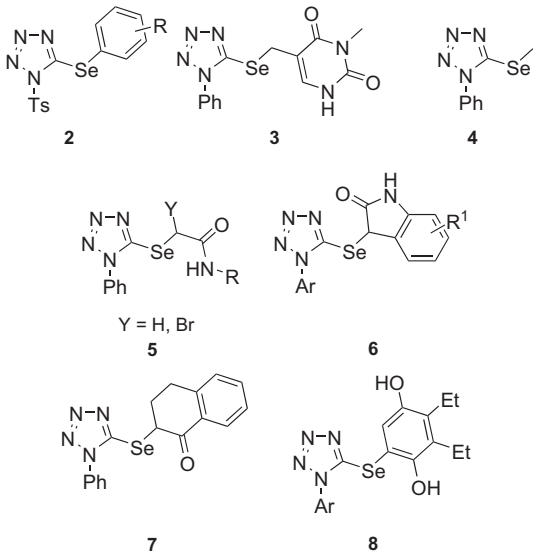


Fig. 1. Structures of known 1-substituted 5-alkyl/arylselanyl-1*H*-tetrazoles.

1-Substituted 5-alkyl/arylselanyl-1*H*-tetrazoles can be also prepared using double alkylation of sodium selenide. The major disadvantage of these reactions lies in low selectivity, which causes the formation of symmetrical selenides and low yields of the desired products. 5-{[(1-Phenyl-1*H*-tetrazol-5-yl)selanyl]methyl} uracil and its methyl derivative **3** were prepared using this protocol.[21] 5-Methylselanyl-1-phenyl-1*H*-tetrazole (**4**) was prepared from 5-chloro-1-phenyl-1*H*-tetrazole by its reaction with bis(methoxymagnesium)diselenide in methanol. However, the target product was obtained in 14% yield only.[22] Compounds with structures **5**–**8** and some of their derivatives were described in patents connected with the development of photographic light-sensitive materials.[23–25]

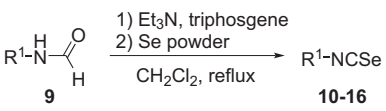
To investigate these sulfur/selenium bioisosteres in greater detail, a general method of 1-substituted 5-alkyl/arylselanyl-1*H*-tetrazoles synthesis, using easily available reactants and a simple experimental procedure, is needed.

In this study we explored the possibility of the synthesis of 1-alkyl/aryl-5-alkylselanyl-1*H*-tetrazoles starting from alkyl/arylisoselenocyanates, analogous with the simplest and most successful approaches for the synthesis of 1-substituted 5-alkyl/arylsulfanyl-1*H*-tetrazoles,[14,26–28] starting from the corresponding alkyl/arylisothiocyanates. This involved both two-step and one-pot procedures under various conditions including phase-transfer catalysis.

2. Results and discussion

The starting alkyl/arylisoselenocyanates **10**–**16** were prepared by a one-pot reaction from the corresponding *N*-alkyl/arylformamides **9** (Table 1).[29] The reaction proceeded through the formation of an isonitrile, which than reacted with selenium to form an isoselenocyanate. These compounds are an advantageous starting material for the synthesis of different organoselenium compounds because of their simple synthesis and safety handling and storage.

Table 1
Preparation of alkyl/arylisoselenocyanates **10**–**16**.



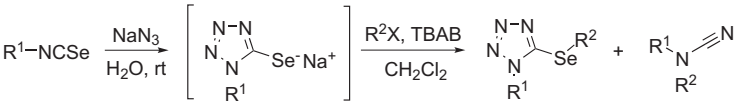
Entry	Product	R^1	Yield [%]
1	**10**	Ph–	63
2	**11**	4-MeOPh–	68
3	**12**	4-BrPh–	58
4	**13**	$CH_3(CH_2)_3$–	67
5	**14**	$CH_3(CH_2)_5$–	43
6	**15**	C_6H_{11}–	98
7	**16**	$CH_3(CH_2)_7$–	67

First, we attempted to synthesize 1-substituted-1*H*-tetrazole-5-selenols from the corresponding isoselenocyanates. To find suitable conditions for the preparation of 1-substituted-1*H*-tetrazole-5-selenols, we treated phenylisoselenocyanate (**10**) with sodium azide in various solvents (H_2O, CH_3OH, C_2H_5OH, CH_3CN, THF, DMF, CH_3NO_2, Et_3N, CH_2Cl_2/H_2O), with tetrabutylammonium azide (TBAA) or $Et_3N\cdot HN_3$ in toluene or CH_2Cl_2, with Me_3SnN_3 in toluene, THF, CH_3CN or CH_2Cl_2 and also with Me_3SiN_3 itself. Unfortunately all these reactions led to decomposition with precipitation of selenium powder, confirming that many nucleophilic selenium species are highly reactive and usually cannot be isolated.[30] Nevertheless, reaction of cyclohexylisoselenocyanate (**15**) with sodium azide in water was successful and sodium 1-cyclohexyl-1*H*-tetrazole-5-selenolate was isolated as a mixture with residual sodium azide. Unfortunately, acidification of sodium 1-cyclohexyl-1*H*-tetrazole-5-selenolate led to precipitation of red selenium at pH 5.5–6.

As tetrazole-5-selenolates were sensitive to acidification, we decided to alkylate them without isolation under the conditions of phase-transfer catalysis with tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst (method 1, Table 2). Reaction of alkylisoselenocyanates **13**–**15** with sodium azide followed by addition of an alkylating agent under the condition of phase-transfer catalysis led to the formation of the intended 1-alkyl-5-alkyl selanyl-1*H*-tetrazoles (**23a**, **25a**, **26a**, **31a**, **33a**, and **34a**) as the only products, but only in low-to-moderate yields (11–50%). In the case of aryl derivatives, the target compounds (**17**–**19a**, **21a**) were formed in very low yields (5–14%), due to an unexpected formation of *N*-alkyl-*N*-arylcyanamides (**17**–**19b**) as the main products. Moreover, reaction of 4-bromophenylisoselenocyanate (**12**) led to complex mixture of products. In the case of alkyl derivatives, the formation of *N*,*N*-disubstituted cyanamides was not observed.

These results encouraged us to carry out one-pot reactions in an attempt to immediately alkylate tetrazole-5-selenolate before its decomposition. Reactions of phenylisoselenocyanate (**10**) and 4-methoxyphenylisoselenocyanate (**11**) with benzyl bromide and

Table 2
Synthesis of 1-alkyl/aryl-5-alkylselanyl-1*H*-tetrazoles prepared from alkyl/arylisoselenocyanates **10**–**15** by method 1



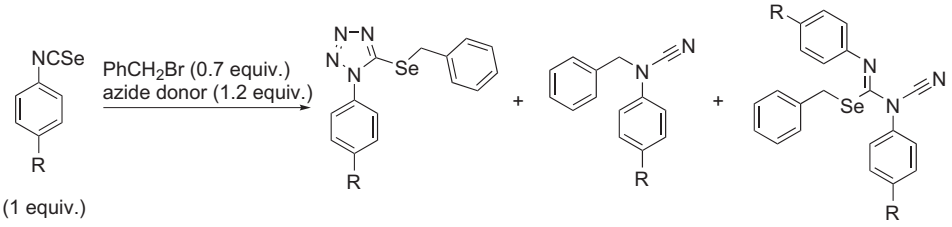
Entry	Substrate	R^1	R^2	X	Product	Yield [%]	
						a	**b**
1	**10**	Ph–	$PhCH_2$–	–Br	**17**	5	52
2	**11**	4-CH_3OPh–	$PhCH_2$–	–Br	**18**	5	49
3	**10**	Ph–	3,5-$(NO_2)_2PhCH_2$–	–Cl	**19**	14	57
4	**12**	4-BrPh–	3,5-$(NO_2)_2PhCH_2$–	–Cl	**21**	5	—
5	**13**	$CH_3(CH_2)_3$–	$PhCH_2$–	–Br	**23**	11	0
6	**14**	$CH_3(CH_2)_5$–	CH_3–	–OSO_3CH_3	**25**	17	0
7	**14**	$CH_3(CH_2)_5$–	$PhCH_2$–	–Br	**26**	15	0
8	**15**	C_6H_{11}–	CH_3–	–OSO_3CH_3	**31**	44	0
9	**15**	C_6H_{11}–	3,5-$(NO_2)_2PhCH_2$–	–Cl	**33**	47	0
10	**15**	C_6H_{11}–	2,4-$(NO_2)_2PhCH_2$–	–Cl	**34**	50	0

azide in different solvents were accomplished to find suitable conditions for the synthesis of 5-alkylselanyl-1-aryl-1*H*-tetrazoles (Table 3).

As shown in Table 3, almost all reactions of substrate **10** led again to the formation of the target product **17a** together with cyanamide **17b**, as in the case of method 1. Furthermore, another unexpected side product was found, confirmed to be (*Z*)-*Se*-benzyl-*N*-cyano-*N*,*N*′-diphenylisoselenourea (**17c**) by NMR and X-ray crystallography experiments (Fig. 2). The highest yields of 5-benzylselanyl-1-phenyl-1*H*-tetrazole (**17a**) were achieved in THF or CH_3CN, both with a small amount of water, at rt (Table 3, entries 4 and 7).

However, the main products of all these reactions were *N*-benzyl-*N*-phenylcyanamide (**17b**) or (*Z*)-Se-benzyl-*N*-cyano-*N*,*N*′-diphenylisoselenourea (**17c**). The reaction of the substrate **11** proceeded similarly, 5-benzylselanyl-1-(4-methoxyphenyl)-1*H*-tetrazole (**18a**), *N*-benzyl-*N*′-(4-methoxyphenyl)cyanamide (**18b**), and (*Z*)-*Se*-benzyl-*N*-cyano-*N*,*N*′-bis(4-methoxyphenyl)isoselenourea

Table 3
One-pot reactions of arylisoselenocyanates **10** and **11** with azide anion under various reaction conditions



Entry	Substrate	Solvent	Water [%]	Azide donor	Temp	Product	Yield [%]		
							a	**b**	**c**
1	**10**	H_2O	—	NaN_3	rt	**17**	4	0	56
2	**10**	1,4-Dioxane	5	NaN_3	rt	**17**	10	71	0
3	**10**	1,4-Dioxane	50	NaN_3	rt	**17**	3	56	0
4	**10**	THF	5	NaN_3	rt	**17**	22	47	10
5	**10**	THF	5	NaN_3	−45 °C	**17**	5	65	2
6	**10**	THF	—	TBAA	rt	**17**	5	Trace	23
7	**10**	CH_3CN	5	NaN_3	rt	**17**	17	12	19
8	**10**	CH_3CN	5	NaN_3	−45 °C	**17**	7	51	3
9	**10**	CH_3CN	—	NaN_3	rt	**17**	16	4	56
10[a]	**10**	CH_2Cl_2	50	NaN_3	rt	**17**	4	1	64
11	**10**	C_6H_5N	5	NaN_3	rt	**17**	Decomposition		
12	**10**	$(CH_3)_3SiN_3$	—	$(CH_3)_3SiN_3$	rt	**17**	Decomposition		
13	**11**	H_2O	—	NaN_3	rt	**18**	0	0	62
14[b]	**11**	H_2O	—	NaN_3	rt	**18**	1	10	23
15	**11**	THF	5	NaN_3	rt	**18**	43	47	Trace
16	**11**	THF	—	Me_3SiN_3	−60 °C	**18**	0	16	0
17	**11**	THF	—	TBAA	rt	**18**	10	28	18
18	**11**	CH_3CN	5	NaN_3	rt	**18**	45	21	20
19	**11**	DMF	5	NaN_3	rt	**18**	27	27	Trace
20[a]	**11**	CH_2Cl_2	50	NaN_3	rt	**18**	Trace	38	40

[a] Tetrabutylammonium bromide (TBAB) was used as phase-transfer catalyst.
[b] Compound **11** was reacted with sodium azide and pyridine (1:1.2:3 molar ratio) in water for 3 h at rt, followed by addition of benzyl bromide (in 0.7 molar ratio) in THF. Reaction mixture was stirred overnight.

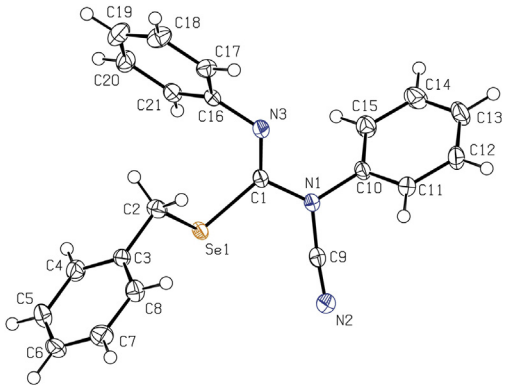
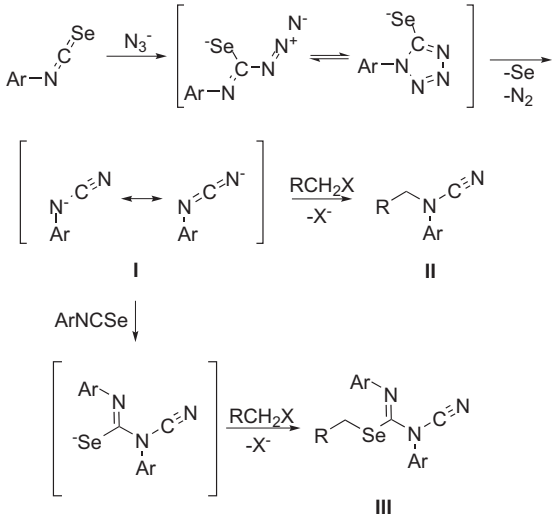


Fig. 2. The molecular structure (ORTEP 50% probability level) of isoselenourea **17c**. Selected interatomic distances [Å], angles and interplanar angle [°]: Se1–C1 1.9394(16), Se1–C2 1.9830(16), C1–N1 1.419(2), C1–N3 1.257(2), N1–C9 1.346(2), C9–N2 1.147(2); C1–Se1–C2 100.29(7), Se1–C1–N1 112.29(11), Se1–C1–N3 130.25(12), C1–N1–C9 121.53(13), C1–N3–C16 123.17(14), N1–C9–N2 175.03(18); Se1–C1–N3 versus C9–N1–C10 10.90(3).

(**18c**) were formed almost under any conditions. The highest yields of the target tetrazole **18a** were again achieved in THF or CH_3CN with a small amount of water (Table 3, entries 15 and 18). Interestingly, when one-pot reactions under phase-transfer catalysis or in water were performed, the target tetrazoles **17a** and **18a** were formed either in trace amounts or were not formed at all. As Table 3 demonstrates, variations in the obtained yields are high and hardly predictable.

It should be noted that reactions in dry solvents and in a mixture of organic solvent/water, 1:1 (v/v) proceeded with slightly lower yields than in the case of using approx. 5% of water to dissolve sodium azide before its addition to reaction mixture.

The formation of the unexpected *N*-alkyl-*N*-arylcyanamides and (*Z*)-*Se*-alkyl-*N*-cyano-*N*,*N*′-diarylisoselenoureas explains the release of elemental selenium in all these reactions. We suggest that after the addition of the azide anion to arylisoselenocyanate, nitrogen together with selenium could be released and sodium *N*-cyano-*N*-arylamide (**I**) formed (Scheme 2). This anion could be subsequently alkylated to form *N*-alkyl-*N*-arylcyanamide (**II**) or it could react with another molecule of arylisoselenocyanate and, after alkylation, produce (*Z*)-*Se*-alkyl-*N*-cyano-*N*,*N*′-diarylisoselenourea (**III**).



Scheme 2. Formation of side products of the reactions of arylisoselenocyanates with azide anion.

Based on the aforementioned results we decided to use THF (method 2) or CH_3CN (method 3) as the solvents, both with 5% added water, for the synthesis of a series of 1-substituted-5-alkylselanyl-1*H*-tetrazoles. Moreover, the results achieved by these two methods were compared with yields obtained by the one-pot reactions under phase-transfer catalysis (method 4), which proceeded with the highest yields of the side products, *N*-alkyl-*N*-arylcyanamides and (*Z*)-*Se*-alkyl-*N*-cyano-*N*,*N*′-diarylisoselenoureas. Special attention was paid to the synthesis of 1-substituted-5-[(dinitrobenzyl) selanyl]-1*H*-tetrazoles, because many previous studies showed high antimycobacterial activity of related mono/dinitro substituted compounds.[31–34]

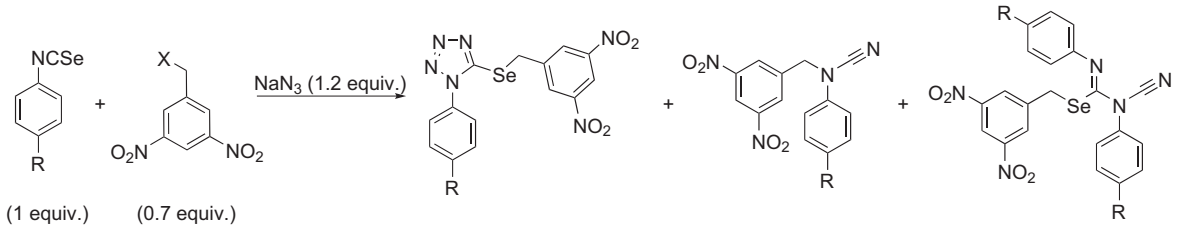
The results of the reactions of arylisoselenocyanates **10**–**12** are summarized in Table 4. The target 1-aryl-5-[(3,5-dinitrobenzyl) selanyl]-1*H*-tetrazoles (**19**–**21a**) were prepared as in previous cases in low-to-moderate yields, which were not increased even by utilization of 3,5-dinitrobenzyl iodide. Changes in the solvent system as well as in the azide donor led again to a decrease in the yields of products (e.g., product **19a** was obtained in 21% yield by the reaction of substrate **10** with 3,5-dinitrobenzyl iodide and sodium azide in the mixture of CH_3CN/H_2O, 1:1, the side products **19b** and **19c** were obtained in 39 and 11%, respectively; while the reaction of substrate **11** with 3,5-dinitrobenzyl iodide and TBAA in THF led to formation of cyanamide **20b** as the only product). In the case of the one-pot phase-transfer catalyzed reaction (Table 4, method 4), 3,5-dinitrobenzyl iodide had to be used to obtain reasonable yields. As all the reactions at temperatures below 0 °C led to the formation of cyanamides as the main products, we decided to carry out the reaction of 4-bromophenylisoselenocyanate with sodium azide and 3,5-dinitrobenzyl iodide in THF at 55 °C. In this case, 1-(4-bromo phenyl)-5-[(3,5-dinitrobenzyl)selanyl]-1*H*-tetrazole (**21a**) was isolated in 23% yield, and cyanamide **21b** in 45% yield. Unfortunately, none of the modifications of the reaction conditions or reactant ratios improved the yields of the target 5-alkylselanyl-1-aryl-1*H*-tetrazoles. Thus methods 2 and 3 are the methods of choice for the preparation of 1-substituted-5-alkylselanyl-1*H*-tetrazoles.

The results of the reactions of alkylisoselenocyanates **13**–**16** are summarized in Table 5. In contrast to their aryl analogues, 1-alkyl-5-alkylselanyl-1*H*-tetrazoles **22**–**34** were prepared in good yields using one-pot reactions (methods 2 and 3), which are complete in 30 min to 3 h. Surprisingly, neither *N*,*N*-dialkyl cyanamides nor *Se*-alkyl-*N*-cyano-*N*,*N*′-dialkylisoselenoureas were found regardless of the method used. Tetrabutylammonium azide was also used instead of sodium azide, but, as in the above-mentioned cases, this change did not increase the product yields; tetrazole **32** was prepared in 46% and its dinitro analogue **33** was not formed at all—inseparable mixture of side products was formed.

In this work we demonstrated the enhanced reactivity of alkyl/arylisoselenocyanates toward azide anion compared to alkyl/arylisothiocyanates. Whereas reactions of alkyl/arylisothiocyanates with azide anion lead exclusively to the formation of 1-alkyl/aryl-1*H*-tetrazole-5-thiols, which can be further alkylated,[28] 1-alkyl/aryl-1*H*-tetrazole-5-selenols are unstable compounds and only 1-cyclohexyl-1*H*-tetrazole-5-selenol was partially isolated as its sodium salt. The attempts to alkylate sodium 1-alkyl/aryl-1*H*-tetrazole-5-selenolates in situ under phase-transfer catalysis conditions led to the formation of 1-alkyl-5-alkylselanyl-1*H*-tetrazoles in moderate yields, but 1-aryl-5-alkylselanyl-1*H*-tetrazoles were formed only in very low yields due to unexpected formation of *N*-alkyl-*N*-arylcyanamides (Table 2).

One-pot reactions of alkyl/arylisoselenocyanates with an azide donor and alkylating agent significantly increased the yields of target 1-substituted-5-alkylselanyl-1*H*-tetrazoles. In the case of alkyl derivatives, good yields of the products **22**–**34** were achieved (Table 5). In the case of aryl derivatives, the target tetrazoles **17**–**21a** were formed in low-to-moderate yields (Tables 3 and 4),

Table 4
Reactions of arylisoselenocyanates **10**–**12** with sodium azide and 3,5-dinitrobenzyl halide by methods 2, 3, and 4



10 R = H
11 R = -OCH_3
12 R = -Br

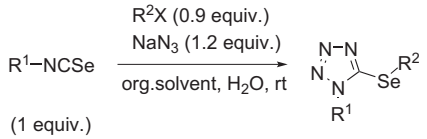
19a R = H
20a R = -OCH_3
21a R = -Br

19b R = H
20b R = -OCH_3
21b R = -Br

19c R = H
20c R = -OCH_3
21c R = -Br

Substrate	Product	Yield [%]				
		Method 2		Method 3		Method 4
		X=Cl	X=I	X=Cl	X=I	X=I
10	**19a**	15	28	28	30	16
10	**19b**	33	31	8	17	27
10	**19c**	2	15	2	32	22
11	**20a**	33	19	33	5	Trace
11	**20b**	40	62	60	44	43
11	**20c**	5	19	0	4	16
12	**21a**	12	34	5	11	17
12	**21b**	0	20	0	15	26
12	**21c**	0	0	0	36	20

Table 5
Synthesis and yields of 1-alkyl-5-alkylselanyl-1*H*-tetrazoles (**22**–**34**) prepared by methods 2, 3, and 4



13-16 **22-34**

R^2 = CH_3, X = OSO_3CH_3; R^2 = $PhCH_2$, X = Br; R^2 = 3,5-$(NO_2)_2PhCH_2$, X = Cl

Substrate	Product	R^1	R^2	Yield [%]		
				Method 2	Method 3	Method 4
13	**22**	$CH_3(CH_2)_3$–	CH_3–	50	59	—
13	**23**	$CH_3(CH_2)_3$–	$PhCH_2$–	73	—	—
13	**24**	$CH_3(CH_2)_3$–	3,5-$(NO_2)_2PhCH_2$–	44	66	54
14	**25**	$CH_3(CH_2)_5$–	CH_3–	57	41	—
14	**26**	$CH_3(CH_2)_5$–	$PhCH_2$–	58	84	61
14	**27**	$CH_3(CH_2)_5$–	3,5-$(NO_2)_2PhCH_2$–	30	45	25
16	**28**	$CH_3(CH_2)_7$–	CH_3–	54	48	—
16	**29**	$CH_3(CH_2)_7$–	$PhCH_2$–	56	74	—
16	**30**	$CH_3(CH_2)_7$–	3,5-$(NO_2)_2PhCH_2$–	38	71	—
15	**31**	C_6H_{11}–	CH_3–	73	—	—
15	**32**	C_6H_{11}–	$PhCH_2$–	76	65	30
15	**33**	C_6H_{11}–	3,5-$(NO_2)_2PhCH_2$–	38	68	57
15	**34**	C_6H_{11}–	2,4-$(NO_2)_2PhCH_2$–	[a]	[a]	[a]

[a] Unseparable mixture. TLC showed the formation of **34** in insignificant amount only.

because these reactions again proceeded via the formation of *N*-alkyl-*N*-arylcyanamides (**17**–**21b**) and, surprisingly, (*Z*)-*Se*-alkyl-*N*-cyano-*N*,*N*′-diarylisoselenoureas (**17**–**21c**) as the main products.

In general, alkyl substituents stabilized the 1-alkyl-1*H*-tetrazole-5-selenolates formed after the addition of the azide anion to isoselenocyanates and facilitated the formation of 1-alkyl-5-alkylselanyl-1*H*-tetrazoles. On the other hand, aryl substituents facilitated the decomposition of 1-aryl-1*H*-tetrazole-5-selenolates leading to the formation of side products, *N*-alkyl-*N*-arylcyanamides and (*Z*)-*Se*-alkyl-*N*-cyano-*N*,*N*′-diarylisoselenoureas.

Furthermore, isoselenoureas **17c** and **19c** (Figs. 2 and 3) were characterized using X-ray crystallography. Both compounds crystallized in the triclinic space group *P*-1, isoselenourea **17c** with two molecules within the unit cell, while its dinitro analogue **19c** crystallized with two independent molecules and with four molecules within the triclinic unit cell. To the best of our knowledge, analogous structures are still elusive in the literature; only several cyclic isoselenoureas (e.g., A,[35,36] B,[37,38] C,[39,40] D,[41,42] E,[35,43] F,[44,45] G[46,47]), which resemble the structural motif of compounds **17c** and **19c**, were found within the crystallographic database (Fig. 4). These compounds reveal rather similar distances and angles of interest within various ring arrangements to the isoselenoureas **17c** and **19c**. The lack of conjugation is seen from the separation of C and N atoms in both molecules of **17c** and **19c**, and thus the double

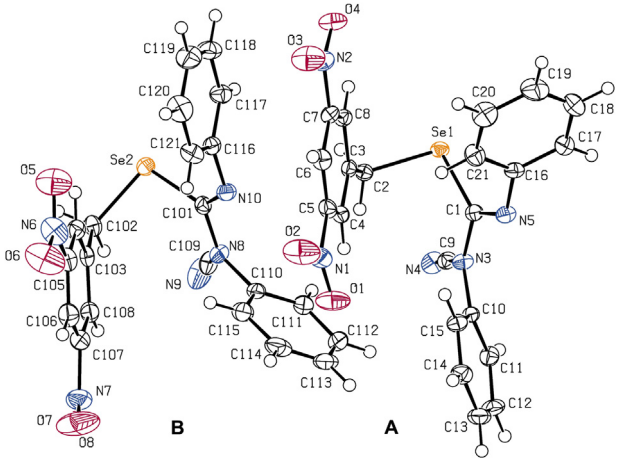


Fig. 3. The molecular structure (ORTEP 50% probability level) of isoselenourea **19c**. Selected interatomic distances [Å], angles and interplanar angle [°] for molecules **A** and **B** (appropriate parameters are given in parentheses): Se1–C1 1.934(2) (1.930(2)), Se1–C2 1.9737(19) (1.972(2)), C1–N3 1.427(2) (1.421(3)), C1–N5 1.255(3) (1.256(3)), N3–C9 1.347(3) (1.343(3)), C9–N4 1.145(3) (1.143(3)); C1–Se1–C2 97.62(8)(97.65(8)), Se1–C1–N3 114.71(14) (115.44(14)), Se1–C1 N5 127.31(15) (126.86(16)), C1–N3–C9 119.91(16) (120.78(17)), C1–N5–C16 123.19(18) (122.73(18)), N3–C9–N4 175.9(2); Se1–C1–N5 versus C9–N3–C10 22.28(2) (16.76(3)).

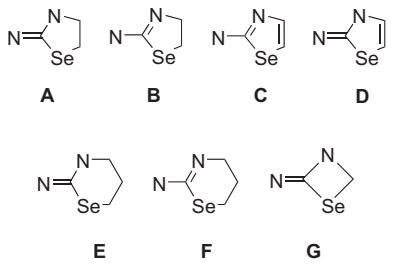


Fig. 4. Structural motifs of compounds similar to isoselenoureas **17c** and **19c** found in the crystallographic database.

and triple bonds between carbon and nitrogen can be surely assigned (Figs. 2 and 3).

In the crystal packing of isoselenoureas **17c** and **19c** (Figs. 5 and 6), no structurally interesting interatomic nor π–π interactions were observed. On the other hand, along the *a*-axis, an intriguing supramolecular architecture is detected. In the case of **17c**, a dimer-like structure is formed (Fig. 5), while in the case of **19c**, its molecules are mutually oriented in layers (Fig. 6) with alternating domains of selenium and oxygen atoms.

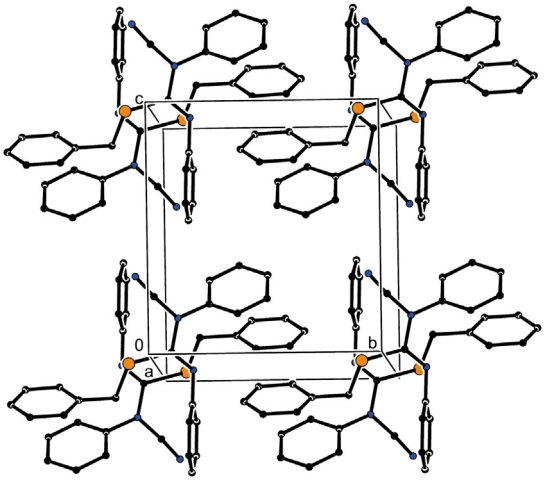


Fig. 5. Crystal packing of isoselenourea **17c** view along axis *a*.

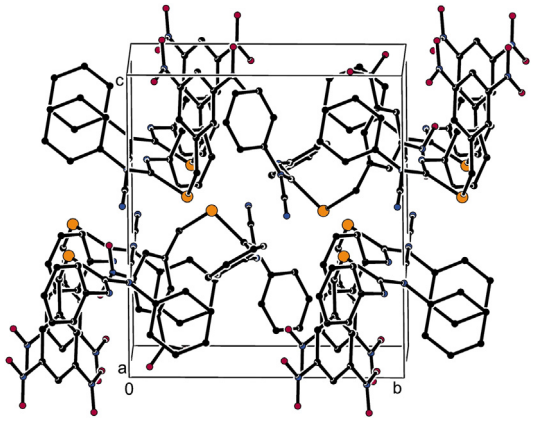


Fig. 6. Crystal packing of isoselenourea **19c** view along axis *a*.

3. Conclusions

In this work, the synthesis of 1-substituted-5-alkylselanyl-1*H*-tetrazoles from alkyl/arylisoselenocyanates has been described. One-pot reactions of arylisoselenocyanates with sodium azide and an alkylating agent led unexpectedly to the formation of *N*-alkyl-*N*-arylcyanamides and (*Z*)-*Se*-alkyl-*N*-cyano-*N*,*N*′-diaryliso selenoureas as the main products, while 1-aryl-5-alkylselanyl-1*H*-tetrazoles were formed only in low yields. Nevertheless, when alkylisoselenocyanates were utilized as the substrates, the reactions led exclusively to the formation of 1-alkyl-5-alkylselanyl-1*H*-tetrazoles in good yields.

Simple and general methods described in this work bring new possibilities for the synthesis of these selenium-containing compounds and can be used in the synthesis and further investigations of biologically active sulfur/selenium bioisosteres.

4. Experimental section

4.1. General

All chemicals for synthesis were obtained from Sigma–Aldrich (Schnelldorf, Germany) and used as received. TLC was performed on Merck aluminum sheets with silica gel 60 F_{254} and/or Merck aluminum sheets with silica gel 60 RP-18 F_{254}s. Merck Kieselgel 60 (0.040–0.063 mm) and/or Merck LiChroprep RP-18 (0.015–0.025 mm) were used for column chromatography. Melting points were recorded on a Büchi B-545 apparatus and are uncorrected. Infrared spectra were measured on a Nicolet 6700 (ATR mode). ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury Vx BB 300 or VNMR S500 NMR spectrometers. Chemical shifts were reported as δ values in parts per million (ppm) and were indirectly referenced to tetramethylsilane (TMS) via the solvent signal. The elemental analysis was carried out on Automatic Microanalyser EA1110CE (Fisons Instruments S.p.A., Milano, Italy). Electrospray ionization mass spectroscopic (ESI MS) experiments were performed using Acquity UPLC with MS/MS Quattro Micro detection (Micromass+Waters). High-resolution mass spectra were recorded on VG-Analytical ZAB-SEQ.

4.2. Crystallography

The X-ray data for the colorless and yellowish crystals of isoselenoureas **17c** and **19c** were obtained at 150 K using an Oxford Cryostream low-temperature device on a Nonius KappaCCD diffractometer with Mo Kα radiation (λ=0.71073 Å), a graphite monochromator, and the ϕ and χ scan mode. Data reductions were performed with DENZO-SMN.[48] The absorption was corrected by integration methods.[49] Structures were solved by direct methods (Sir92)[50] and refined by full matrix least-square based on F^2 (SHELXL97).[51] Hydrogen atoms were mostly localized on a difference Fourier map, however, to ensure uniformity of treatment of crystal, all hydrogens were recalculated into idealized positions (riding model) and assigned temperature factors $H_{iso}(H)$=1.2 U_{eq}(pivot atom) with C–H=0.97 and 0.93 Å for methylene and hydrogen atoms in aromatic rings.

$R_{int} = \sum\left|F_o^2 - F_{o,mean}^2\right| / \sum F_o^2$, GOF $= [\sum(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{1/2}$ for all data, $R(F) = \sum||F_o| - |F_c||/\sum|F_o|$ for observed data, $wR(F^2) = [\sum(w(F_o^2 - F_c^2)^2)/(\sum w(F_o^2)^2)]^{1/2}$ for all data.

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 928734 and 928735 for **17c** and **19c**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EY, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or website: http://www.ccdc.cam.ac.uk).

Single crystals of isoselenoureas **17c** and **19c** were of sufficient quality for X-ray diffraction techniques. The crystallographic data and structure refinement parameters for compound **17c** are:

$C_{21}H_{17}N_3Se$, M=390.34, triclinic, *P*-1, *a*=9.0471(5) Å, *b*=10.6140(5) Å, *c*=10.6470(3) Å, α=83.622(4)°, β=68.472(3)°, γ=68.326(4)°, *Z*=2, *V*=883.47(8) Å^3, D_c=1.467 g cm^{-3}, μ=2.133 mm^{-1}, T_{min}/T_{max}=0.519/0.739; $-11\leq h\leq 11$, $-13\leq k\leq 13$, $-13\leq l\leq 13$; 18,954 reflections measured (θ_{max}=27.49°), 18,869 independent (R_{int}=0.0226), 3769 with $I>2\sigma(I)$, 226 parameters, *S*=1.098, *R*1(obsd data)=0.0246, *wR*2(all data)=0.0612; max., min. residual electron density=0.527, −0.775 e Å^{-3}.

Crystallographic data for compound **19c**: $C_{21}H_{15}N_5O_4Se$, *M*=480.34, triclinic, *P*-1, *a*=12.7870(9) Å, *b*=13.1701(10) Å, *c*=14.4670(9) Å, α=78.456(6)°, β=68.953(4)°, γ=63.744(6)°, *Z*=4, *V*=2036.7(3) Å^3, D_c=1.566 g cm^{-3}, μ=1.883 mm^{-1}, T_{min}/T_{max}=0.549/0.772; $-16\leq h\leq 16$, $-17\leq k\leq 17$, $-18\leq l\leq 18$; 44,792 reflections measured (θ_{max}=27.5°), 44,722 independent (R_{int}=0.0296), 7683 with $I>2\sigma(I)$, 559 parameters, *S*=1.116, *R*1(obsd data)=0.0298, *wR*2(all data)=0.0570; max., min. residual electron density=0.362, −0.382 e Å^{-3}.

4.3. Synthesis of alkyl/arylisoselenocyanates (10–16)

*4.3.1. Phenylisoselenocyanate (**10**).*[52] To a refluxing mixture of the *N*-phenylformamide (1 g, 8.25 mmol) and triethylamine (3.59 g, 4.95 ml, 35.49 mmol) in CH_2Cl_2 (35 ml) a solution of triphosgene (1.3 g, 4.37 mmol) in CH_2Cl_2 (15 ml) was added dropwise over a period of 1 h. After the addition was complete, the mixture was stirred at reflux for an additional 3 h until the starting material disappeared, as determined by TLC. Selenium powder (1.3 g, 16.5 mmol) was then added, and the mixture was refluxed for an additional 12 h. The formation of isoselenocyanate could be observed by formation of an orange spot on TLC (after oxidation on air). After completion, the mixture was cooled, filtered, and the precipitate on the filter was washed with EtOAc. The organic solution was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (mobile phase: hexane) to give 0.95 g (5.2 mmol, 63%) of **10** as a yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.31 (3H, m), 7.30–7.27 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 129.68, 129.54, 129.31 (NCSe), 128.07, 126.06. IR (KBr): 2110 (s, NCSe), 2049, 1588, 1487, 1070, 907, 845, 748, 683 cm^{-1}.

Isoselenocyanates **11**–**14** and **16** were prepared according to procedure in Section 4.3.1.

*4.3.2. 4-Methoxyphenylisoselenocyanate (**11**).*[53] The refluxing mixture was stirred for 3 h after the addition of the solution of triphosgene in CH_2Cl_2 and then for 6 h after the addition of selenium powder. Mobile phase: hexane/EtOAc, 35:1. Yield: 68% as slightly pink solid; mp 49–50 °C (lit.[53] 50–51 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (2H, d, *J*=9.0 Hz), 6.86 (2H, d, *J*=9.0 Hz), 3.81 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.13, 127.37 (2C, NCSe+Ar), 122.14, 114.79, 55.57. IR (KBr): 2993, 2955, 2930, 2834, 2116 (s, NCSe), 2058, 1877, 1502, 1452, 1441, 1303, 1248, 1166, 1105, 1028, 820, 759, 702 cm^{-1}.

*4.3.3. 4-Bromophenylisoselenocyanate (**12**).*[45] The refluxing mixture was stirred for 4.5 h after the addition of the solution of triphosgene in CH_2Cl_2 and then for 12 h after the addition of selenium powder. Mobile phase: hexane. Yield: 58% as white crystalline solid; mp 80–81 °C. ^{1}H NMR (500 MHz, DMSO): δ 7.66 (2H, d, *J*=8.6 Hz), 7.47 (2H, d, *J*=8.6 Hz); ^{13}C NMR (126 MHz, DMSO): δ 132.98, 129.66 (NCSe), 128.52, 128.31, 121.60. IR (KBr): 3083, 2119 (s, NCSe), 2050, 1479, 1398, 1069, 1011, 845, 816 cm^{-1}. Anal. Calcd for C_7H_4BrNSe: C, 32.22; H, 1.54; N, 5.37. Found: C, 32.03; H, 1.83; N, 5.45.

*4.3.4. Butylisoselenocyanate (**13**).*[54] The refluxing mixture was stirred for 4.5 h after the addition of the solution of triphosgene in CH_2Cl_2 and then for 5.5 h after the addition of selenium powder. Mobile phase: hexane/EtOAc, 30:1. Yield: 67% as slightly yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.59 (2H, t, *J*=6.6 Hz), 1.74–1.67 (2H, m), 1.50–1.41 (2H, m), 0.94 (3H, t, *J*=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 121.82 (NCSe), 45.11, 31.30, 19.66, 13.13. IR (KBr): 2959, 2938, 2873, 2140 (s, NCSe), 1736, 1458, 1446, 1344, 1116, 743 cm^{-1}.

*4.3.5. Hexylisoselenocyanate (**14**).*[55] The refluxing mixture was stirred for 4.5 h after the addition of the solution of triphosgene in CH_2Cl_2 and then for 8 h after the addition of selenium powder. Mobile phase: hexane/EtOAc, 30:1. Yield: 43% as slightly yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.58 (2H, t, *J*=6.6 Hz), 1.75–1.68 (2H, m), 1.45–1.37 (2H, m), 1.36–1.26 (4H, m), 0.89 (3H, t, *J*=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 121.87 (NCSe), 45.42, 30.82, 29.35, 26.12, 22.33, 13.87. IR (KBr): 2955, 2928, 2858, 2138 (s, NCSe), 1449, 1344, 726 cm^{-1}.

*4.3.6. Cyclohexylisoselenocyanate (**15**).*[56] Cyclohexylisoselenocyanate was prepared from commercially available cyclohexyl isocyanide. A mixture of cyclohexyl isocyanide (1 g, 9.16 mmol) and selenium powder (1.45 g, 18.32 mmol) in dry CH_2Cl_2 (15 ml) was stirred at reflux for 3 h. After completion, as determined by TLC, the solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (hexane/EtOAc, 50:1). Yield: 98% (1.69 g, 8.98 mmol) as slightly yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84–3.74 (1H, m), 1.95–1.87 (2H, m), 1.79–1.63 (4H, m), 1.54–1.32 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 121.65 (NCSe), 55.85, 32.65, 24.88, 23.01. IR (KBr): 2933, 2855, 2114 (s, NCSe), 2065, 1448, 1361, 1318, 1126, 1048, 891, 671 cm^{-1}

*4.3.7. Octylisoselenocyanate (**16**).* The refluxing mixture was stirred for 3 h after the addition of the solution of triphosgene in CH_2Cl_2 and then for 5 h after the addition of selenium powder. Mobile phase: hexane/EtOAc, 35:1. Yield: 67% as slightly yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (2H, t, *J*=6.7 Hz), 1.77–1.68 (2H, m), 1.47–1.21 (10H, m), 0.89 (3H, t, *J*=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 121.70 (NCSe), 45.42, 31.64, 29.36, 28.97, 28.65, 26.47, 22.56, 14.03. IR (KBr): 2924, 2855, 2135 (s, NCSe), 1737, 1456, 1343, 1116, 722 cm^{-1}; HRMS *m*/*z* (CI) calcd for $C_9H_{17}NSe+H^+$ ($M+H^+$) 220.0599, found 220.0595.

4.4. Synthesis of 1-alkyl/aryl-5-alkylselanyl-1*H*-tetrazoles

4.4.1. General procedures. Dimethylsulfate, benzyl bromide, 3,5-dinitrobenzyl chloride, and 3,5-dinitrobenzyl iodide were used as alkylating agents.

4.4.2. Method 1. Isoselenocyanate (1 mmol) and sodium azide (1.2 mmol) in water (7 ml) were stirred for 12–24 at rt until completion, as determined by TLC (for R_f values see later). Precipitated selenium was filtered off and the aqueous solution was washed with EtOAc (2×10 ml). The alkylating agent (0.7 mmol) and TBAB (0.035 mmol) in CH_2Cl_2 (7 ml) were added to the aqueous solution. The reaction mixture was gently stirred at rt overnight. The organic phase was separated, washed with water (2×10 ml), and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude products were separated and purified by column chromatography on silica gel.

4.4.3. Method 2. To the solution of isoselenocyanate (1 mmol) and alkylating agent (0.7 mmol for arylisoselenocyanates/0.9 mmol for alkylisoselenocyanates) in THF (10 ml), sodium azide (1.2 mmol) in water (0.5 ml) was added. The reaction mixture was stirred until the starting isoselenocyanate disappeared, as determined by TLC. After completion, the THF was evaporated, the crude product was

dissolved in EtOAc (10 ml), and washed with water (2×10 ml). The organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude products were purified by silica gel column chromatography and/or reverse phase column chromatography (see later).

4.4.4. Method 3. This method is same as method 2, only acetonitrile was used instead of THF.

4.4.5. Method 4. Isoselenocyanate (1 mmol) and alkylating agent (0.7 mmol for arylisoselenocyanates/0.9 mmol for alkylisoselenocyanates) in CH_2Cl_2 (7 ml) and sodium azide (1.2 mmol) in H_2O (7 ml) were stirred in the presence of TBAB (0.035/0.045 mmol for aryl/alkylisoselenocyanate, respectively) at rt until completion (usually overnight). The organic phase was then separated, washed with water (2×10 ml), and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product was purified by column chromatography on silica and/or reverse phase column chromatography (see later).

4.5. 5-Alkylselanyl-1-aryl-1*H*-tetrazoles (17–21b)

Yields of the products are given in Tables 2–4.

Compounds **17a**, **17b**, and **17c** were separated by reverse phase column chromatography, mobile phase: MeCN/H_2O, 2:1.

*4.5.1. 5-Benzylselanyl-1-phenyl-1H-tetrazole (**17a**).* Beige solid; mp 71 °C. R_f (hexane/EtOAc, 3:1) 0.72, R_f (RP-18; MeCN/H_2O, 2:1) 0.27. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55–7.44 (5H, m, Ar), 7.42–7.36 (2H, m, Ar), 7.33–7.24 (3H, m, Ar), 4.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.18, 136.24, 133.94, 130.20, 129.75, 129.11, 128.80, 127.91, 123.88, 32.56. IR (KBr): 3030, 2922, 1595, 1497, 1374, 1233, 1089, 1014, 973, 765, 693 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_4Se$: C, 53.34; H, 3.84; N, 17.77. Found: C, 53.25; H, 3.98; N, 17.53.

*4.5.2. N-Benzyl-N-phenylcyanamide (**17b**).*[57] White crystalline solid; mp 62 °C (lit.[57] 59–60 °C). R_f (hexane/EtOAc, 3:1) 0.75, R_f (RP-18; MeCN/H_2O, 2:1) 0.33. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.30 (7H, m, Ar), 7.17–7.05 (3H, m, Ar), 4.81 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.76, 134.25, 129.62, 129.06, 128.50, 127.31, 123.67, 115.98, 113.90, 53.70. IR (KBr): 3030, 2925, 2216 (s, C≡N), 1599, 1494, 1453, 1367, 1233, 1181, 1078, 930, 878, 766, 718, 686 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 2.81; N, 13.45. Found: C, 80.40; H, 2.52; N, 13.62. LRMS *m*/*z* (ESI) 208.88 (100, MH^+), 209.89 (15%).

*4.5.3. (Z)-Se-Benzyl-N-cyano-N,N′-diphenylisoselenourea (**17c**).* White crystalline solid; mp 97–98 °C. R_f (hexane/EtOAc, 3:1) 0.8, R_f (RP-18; MeCN/H_2O, 2:1) 0.12. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.08 (13H, m, Ar), 6.79–6.71 (2H, m, Ar), 4.05 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.54, 144.34, 137.35, 136.59, 129.55, 129.11, 128.91, 128.74, 128.25, 127.72, 125.03, 124.76, 120.42, 111.20, 31.96. IR (KBr): 2223 (s, C≡N), 1627, 1587, 1486, 1240, 1231, 1187, 1163, 1077, 851, 751, 690 cm^{-1}; HRMS *m*/*z* (ESI) calcd for $C_{21}H_{17}N_3Se+H^+$ ($M+H^+$) 392.06605, found 392.06597. Anal. Calcd for $C_{21}H_{17}N_3Se$: C, 64.62; H, 4.39; N, 10.77. Found: C, 64.58; H, 4.79; N, 10.86.

Compounds **18a**, **18b**, and **18c** were separated by reverse phase column chromatography, mobile phase: MeCN/H_2O, 2:1.

*4.5.4. 5-Benzylselanyl-1-(4-methoxyphenyl)-1H-tetrazole (**18a**).* Yellowish viscous oil. R_f (hexane/EtOAc, 3:1) 0.34, R_f (RP-18; MeCN/H_2O, 2:1) 0.28. ^{1}H NMR (300 MHz, acetone): δ 7.47–7.40 (4H, m, Ar), 7.32–7.20 (3H, m, Ar), 7.17–7.10 (2H, m), 4.64 (2H, s), 3.88 (3H, s); ^{13}C NMR (75 MHz, acetone): δ 161.96, 148.22, 138.71, 129.92, 129.42, 128.40, 127.62, 126.99, 115.71, 56.08, 32.53. IR (KBr): 3062, 2837, 1608, 1515, 1454, 1377, 1258, 1171, 1023, 834, 761, 698 cm^{-1}. LRMS *m*/*z* (ESI) 346.7 (100, MH^+), 344.8 (50), 342.8 (20%); HRMS *m*/*z* (ESI) calcd for $C_{15}H_{14}N_4OSe+H^+$ ($M+H^+$) 347.04056, found 347.04056.

*4.5.5. N-Benzyl-N-(4-methoxyphenyl)cyanamide (**18b**).* White crystalline solid; mp 60 °C. R_f (hexane/EtOA, 3:1) 0.43, R_f (RP-18; MeCN/H_2O, 2:1) 0.41. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.31 (5H, m), 7.05 (2H, d, *J*=9.1 Hz), 6.86 (2H, d, *J*=9.1 Hz), 4.74 (2H, s), 3.77 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.26, 134.47, 133.07, 129.00, 128.47, 127.47, 118.25, 114.83, 55.53, 54.64. IR (KBr): 2956, 2926, 2359, 2212 (s, C≡N), 1509, 1453, 1373, 1291, 1230, 1178, 1019, 821, 740, 703, 684 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.73; H, 6.05; N, 12.03.

*4.5.6. (Z)-Se-Benzyl-N-cyano-N,N′-di(4-methoxyphenyl)isoselenourea (**18c**).* Yellow viscous oil. R_f (hexane/EtOAc, 3:1) 0.35, R_f (RP-18; MeCN/H_2O, 2:1) 0.19. ^{1}H NMR (300 MHz, acetone): δ 7.35–7.20 (7H, m), 7.00 (2H, d, *J*=9.0 Hz), 6.88 (2H, d, *J*=8.8 Hz), 6.78 (2H, d, *J*=9.0 Hz), 4.03 (2H, s), 3.83 (3H, s), 3.76 (3H, s); ^{13}C NMR (75 MHz, acetone): δ 160.69, 157.84, 145.20, 141.90, 138.39, 131.28, 129.82, 129.50, 128.66, 128.31, 122.57, 115.56, 114.86, 111.96, 55.91, 55.64, 32.01; ^{15}N NMR (50.7 MHz, $CDCl_3$): δ 296.5, 214.1, 103.4. IR (KBr): 2956, 2835, 2222 (C≡N), 1621, 1504, 1292, 1242, 1177, 1077, 1031, 831, 697 cm^{-1}. LRMS *m*/*z* (ESI) 451.7 (100, MH^+), 449.8 (52), 452.7 (28), 448.8 (21.5%); HRMS *m*/*z* (ESI) calcd for $C_{23}H_{21}N_3O_2Se+H^+$ ($M+H^+$) 452.08718, found 452.08711.

Compounds **19a**, **19b**, and **19c** were separated by silica gel column chromatography, mobile phase: hexane/EtOAc, 10:1.

*4.5.7. 5-(3,5-Dinitrobenzylselanyl)-1-phenyl-1H-tetrazole (**19a**).* Light beige crystalline solid; mp 141–143 °C (with decomposition). R_f (hexane/EtOAc, 3:1) 0.18. ^{1}H NMR (300 MHz, acetone): δ 8.85 (2H, d, *J*=2.1 Hz), 8.80 (1H, t, *J*=2.1 Hz), 7.78–7.39 (5H, m), 4.95 (2H, s); ^{13}C NMR (75 MHz, acetone): δ 149.29, 147.59, 144.56, 134.88, 131.44, 130.88, 130.46, 125.20, 118.29, 30.39. IR (KBr): 3098, 1536 (NO_2), 1499, 1342 (NO_2), 1232, 1093, 1036, 914, 809, 771, 734, 692, 672 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_6O_4Se$: C, 41.50; H, 2.49; N, 20.74. Found: C, 41.32; H, 2.71; N, 20.47.

*4.5.8. N-(3,5-Dinitrobenzyl)-N-phenylcyanamide (**19b**).* Yellowish solid; mp 174–176 °C. R_f (hexane/EtOAc, 3:1) 0.28. ^{1}H NMR (300 MHz, acetone): δ 8.92 (1H, t, *J*=2.1 Hz), 8.76 (2H, d, *J*=2.1 Hz), 7.46–7.39 (2H, m), 7.31–7.26 (2H, m), 7.18–7.11 (1H, m), 5.38 (2H, s); ^{13}C NMR (75 MHz, acetone): δ 149.76, 140.98, 140.39, 130.78, 128.85, 124.89, 119.28, 116.86, 113.66, 52.39. IR (KBr): 3115, 2921, 2360, 2221 (s, C≡N), 1597, 1538 (NO_2), 1492, 1342 (NO_2), 1234, 1188, 1083, 903, 810, 763, 723, 696, 666 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_4O_4$: C, 56.38; H, 3.38; N, 18.78. Found: C, 56.3; H, 3.56; N, 18.88.

*4.5.9. (Z)-Se-(3,5-Dinitrobenzyl)-N-cyano-N,N′-diphenylisoselenourea (**19c**).* Yellowish solid; mp 130 °C. R_f (hexane/EtOAc, 3:1) 0.39. ^{1}H NMR (300 MHz, acetone): δ 8.81 (1H, t, *J*=2.2 Hz), 8.54 (2H, d, *J*=2.2 Hz), 7.53–7.38 (5H, m), 7.32–7.24 (2H, m), 7.14–7.07 (1H, m), 6.84–6.78 (2H, m), 4.42 (2H, s); ^{13}C NMR (75 MHz, acetone): δ 149.37, 148.32, 144.24, 144.09, 138.50, 130.61, 129.97, 129.77, 129.47, 126.34, 125.59, 121.30, 118.31, 111.33, 30.26. IR (KBr): 3087, 2963, 2922, 2220 (C≡N), 1651, 1592, 1537 (NO_2), 1488, 1343 (NO_2), 1237, 1183, 1076, 912, 853, 809, 754, 695 cm^{-1}. Anal. Calcd for $C_{21}H_{15}N_5O_4Se$: C, 52.51; H, 3.15; N, 14.58. Found: C, 52.46; H, 3.32; N, 14.30; HRMS *m*/*z* (ESI) calcd for $C_{21}H_{15}N_5O_4Se+H^+$ ($M+H^+$) 482.03620, found 482.03618.

Compounds **20a**, **20b**, and **20c** were separated by silica gel column chromatography, mobile phase: hexane/EtOAc, 7:1.

*4.5.10. 5-(3,5-Dinitrobenzylselanyl)-1-(4-methoxyphenyl)-1H-tetrazole (**20a**).* Brownish solid; mp 131–132 °C (with decomposition).

R_f (hexane/EtOAc, 3:1) 0.12. ^{1}H NMR (500 MHz, acetone): δ 8.83 (2H, d, J=2.1 Hz), 8.80 (1H, t, J=2.1 Hz), 7.48 (2H, d, J=9.0 Hz), 7.14 (2H, d, J=9.0 Hz), 4.91 (2H, s), 3.89 (3H, s); ^{13}C NMR (125 MHz, acetone): δ 162.07, 149.27, 147.77, 144.63, 130.42, 127.39, 126.94, 118.26, 115.81, 56.11, 30.26. IR (KBr): 3089, 2923, 1608, 1591, 1537 (NO_2), 1511, 1446, 1342 (NO_2), 1257, 1173, 1020, 913, 839, 730, 672 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_6O_5Se$: C, 41.39; H, 2.78; N, 19.31. Found: C, 41.59; H, 2.41; N, 19.0.

*4.5.11. N-(3,5-Dinitrobenzyl)-N-(4-methoxyphenyl)cyanamide (**20b**).* Yellowish solid; mp 121–122 °C. R_f (hexane/EtOAc, 3:1) 0.24. ^{1}H NMR (500 MHz, acetone): δ 8.91 (1H, t, J=2.1 Hz), 8.73 (2H, d, J=2.1 Hz), 7.23 (2H, d, J=9.2 Hz), 6.97 (2H, d, J=9.2 Hz), 5.28 (2H, s), 3.76 (3H, s); ^{13}C NMR (125 MHz, acetone): δ 157.70, 149.73, 141.15, 133.51, 128.97, 119.37, 119.25, 115.92, 114.53, 55.83, 53.32. IR (KBr): 3091, 2839, 2218 (s, C≡N), 1596, 1545 (NO_2), 1509, 1439, 1344 (NO_2), 1238, 1180, 1025, 913, 821, 729 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_4O_5$: C, 54.88; H, 3.68; N, 17.07. Found: C, 54.65; H, 4.04; N, 16.72.

*4.5.12. (Z)-Se-(3,5-Dinitrobenzyl)-N-cyano-N,N′-di(4-methoxyphenyl)isoselenourea (**20c**).* Yellowish solid; mp 142 °C (with decomposition). R_f (hexane/EtOAc, 3:1) 0.29. ^{1}H NMR (500 MHz, acetone): δ 8.80 (1H, t, J=2.2 Hz), 8.48 (2H, d, J=2.2 Hz), 7.40 (2H, d, J=9.0 Hz), 7.01 (2H, d, J=9.0 Hz), 6.90–6.76 (4H, m), 4.32 (2H, s), 3.83 (3H, s), 3.76 (3H, s); ^{13}C NMR (125 MHz, acetone): δ 160.90, 158.05, 149.35, 144.26, 143.74, 141.20, 131.06, 129.91, 128.73, 122.76, 118.22, 115.68, 114.92, 111.56, 55.96, 55.64, 30.05. IR (KBr): 3112, 2904, 2221 (C≡N), 1625, 1542 (NO_2), 1505, 1342 (NO_2), 1245, 1175, 1076, 1038, 833, 730 cm^{-1}; HRMS m/z (ESI) calcd for $C_{23}H_{19}N_5O_6Se+H^+$ ($M+H^+$) 542.05733, found 542.05739.

Compounds **21a**, **21b**, and **21c** were separated by silica gel column chromatography, mobile phase: hexane/EtOAc, 8:1.

*4.5.13. 1-(4-Bromphenyl)-5-(3,5-dinitrobenzylselanyl)-1H-tetrazole (**21a**).* White solid; mp 154–155 °C (with decomposition). R_f (hexane/EtOAc, 3:1) 0.12. ^{1}H NMR (500 MHz, acetone) δ 8.84 (2H, d, J=2.1 Hz), 8.80 (1H, t, J=2.1 Hz), 7.84 (2H, d, J=8.8 Hz), 7.58 (2H, d, J=8.3 Hz), 4.95 (2H, s); ^{13}C NMR (125 MHz, acetone): δ 148.38, 146.76, 143.59, 133.19, 133.11, 129.57, 126.28, 123.99, 117.40, 29.71. IR (KBr): 3104, 2923, 1530 (NO_2), 1496, 1361, 1340 (NO_2), 1176, 1073, 1007, 841, 731, 674 cm^{-1}. Anal. Calcd for $C_{14}H_9BrN_6O_4Se$: C, 34.73; H, 1.87; N, 17.36. Found: C, 34.93; H, 1.68; N, 17.01.

*4.5.14. N-(4-Bromphenyl)-N-(3,5-dinitrobenzyl)cyanamide (**21b**).* Beige solid; mp 170 °C (with decomposition). R_f (hexane/EtOAc, 3:1) 0.18. ^{1}H NMR (300 MHz, acetone): δ 8.92 (1H, t, J=2.2 Hz), 8.77 (2H, d, J=2.1 Hz), 7.57 (2H, d, J=9.1 Hz), 7.26 (2H, d, J=9.1 Hz), 5.39 (2H, s); ^{13}C NMR (75 MHz, acetone) δ 149.80, 140.53, 139.92, 133.59, 128.99, 119.41, 118.95, 117.09, 113.21, 52.51. IR (KBr): 3149, 2959, 2230 (s, C≡N), 1595, 1492, 1485, 1395, 1283, 1252, 1178, 1074, 1010, 813 cm^{-1}. Anal. Calcd for $C_{14}H_9BrN_4O_4$: C, 44.58; H, 2.41; N, 14.86. Found: C, 44.2; H, 2.71; N, 14.59.

*4.5.15. (Z)-Se-(3,5-Dinitrobenzyl)-N-cyano-N,N′-di(4-bromophenyl) isoselenourea (**21c**).* Beige solid; mp 156–158 °C (with decomposition). R_f (hexane/EtOAc, 3:1) 0.33. ^{1}H NMR (300 MHz, acetone): δ 8.82 (1H, t, J=2.1 Hz), 8.58 (2H, d, J=2.1 Hz), 7.68 (2H, d, J=8.8 Hz), 7.50 (2H, d, J=8.8 Hz), 7.43 (2H, d, J=8.6 Hz), 6.76 (2H, d, J=8.6 Hz), 4.52 (s, 2H); ^{13}C NMR (75 MHz, acetone): δ 149.41, 147.57, 144.97, 144.03, 137.66, 133.68, 132.73, 129.95, 128.61, 123.53, 122.78, 118.37, 118.32, 110.95, 30.60. IR (KBr): 3101, 2923, 2234 (C≡N), 1616, 1539 (NO_2), 1487, 1344 (NO_2), 1184, 1071, 1013, 913, 825, 730, 672 cm^{-1}. Anal. Calcd for $C_{21}H_{13}Br_2N_5O_4Se$: C, 39.53; H, 2.05; N, 10.97. Found: C, 39.91; H, 2.43; N, 10.76; HRMS m/z (ESI) calcd for $C_{21}H_{13}Br_2N_5O_4Se+Na^+$ ($M+Na^+$) 659.83917, found 659.83855.

4.6. 1-Alkyl-5-alkylselanyl-1*H*-tetrazoles (22–34)

Yields of the products are given in Tables 2 and 5.

*4.6.1. 1-Butyl-5-methylselanyl-1H-tetrazole (**22**).* Yellowish viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.24 (2H, t, J=7.2 Hz), 2.72 (3H, s), 1.92–1.82 (2H, m), 1.42–1.30 (2H, m), 0.96 (3H, t, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.45, 47.70, 31.14, 19.57, 13.36, 8.13. IR (KBr): 2960, 2935, 2874, 2218 (w), 1458, 1428, 1383, 1275, 1186, 1078, 978, 925, 753 cm^{-1}. LRMS m/z (ESI) 220.7 (100, MH^+), 218.9 (52), 216.8 (20%); HRMS m/z (ESI) calcd for $C_6H_{12}N_4Se+H^+$ ($M+H^+$) 221.02999, found 221.02997.

*4.6.2. 5-Benzylselanyl-1-butyl-1H-tetrazole (**23**).* Yellowish viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.19 (5H, m), 4.51 (2H, s), 4.05 (2H, t, J=7.2 Hz), 1.74–1.59 (2H, m), 1.14–1.26 (2H, m), 0.85 (3H, t, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.91, 136.72, 128.93, 128.81, 127.92, 47.67, 32.91, 31.20, 19.46, 13.30. IR (KBr): 2960, 2873, 1495, 1454, 1426, 1381, 1183, 1070, 979, 760, 697 cm^{-1}. LRMS m/z (ESI) 296.8 (100, MH^+), 294.8 (49), 292.9 (18%); HRMS m/z (ESI) calcd for $C_{12}H_{16}N_4Se+H^+$ ($M+H^+$) 297.06129, found 297.06131.

*4.6.3. 1-Butyl-5-(3,5-dinitrobenzylselanyl)-1H-tetrazole (**24**).* White solid; mp 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (1H, t, J=2.0 Hz), 8.69 (2H, d, J=2.1 Hz), 4.77 (2H, s), 4.20 (2H, t, J=7.2 Hz), 1.94–1.67 (2H, m), 1.40–1.15 (2H, m), 0.93 (3H, t, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.52, 145.00, 142.05, 129.43, 118.13, 47.97, 31.18, 29.66, 19.54, 13.31. IR (KBr): 3103, 2965, 2877, 1537 (NO_2), 1428, 1343 (NO_2), 1194, 1075, 987, 915, 810, 731, 677 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_6O_4Se$: C, 37.41; H, 3.66; N, 21.82. Found: C, 37.5; H, 4.0; N, 21.75.

*4.6.4. 5-Methylselanyl-1-hexyl-1H-tetrazole (**25**).* Yellowish viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (2H, t, J=7.2 Hz), 2.70 (3H, s), 1.94–1.79 (2H, m), 1.41–1.15 (6H, m), 0.94–0.79 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.43, 47.96, 30.97, 29.12, 25.95, 22.33, 13.87, 8.12. IR (KBr): 2955, 2931, 2859, 2213 (w), 1457, 1427, 1382, 1275, 1180, 1082, 925, 728, 659 cm^{-1}. LRMS m/z (ESI) 248.8 (100, MH^+), 246.9 (52), 244.9 (21%); HRMS m/z (ESI) calcd for $C_8H_{16}N_4Se+H^+$ ($M+H^+$) 249.06129, found 249.06131.

*4.6.5. 5-Benzylselanyl-1-hexyl-1H-tetrazole (**26**).* Yellowish viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.23 (5H, m), 4.55 (2H, s), 4.08 (2H, t, J=7.2 Hz), 1.78–1.68 (2H, m), 1.29–1.19 (6H, m), 0.86 (3H, t, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.93, 136.71, 128.91, 128.80, 127.92, 47.96, 32.89, 30.92, 29.20, 25, 87, 22.30, 13.87. IR (KBr): 2930, 2858, 1495, 1454, 1426, 1381, 1178, 1069, 760, 697 cm^{-1}. LRMS m/z (ESI) 324.8 (100, MH^+), 322.8 (52), 326.9 (19%); HRMS m/z (ESI) calcd for $C_{14}H_{20}N_4Se+H^+$ ($M+H^+$) 325.09260, found 325.09262.

*4.6.6. 5-(3,5-Dinitrobenzylselanyl)-1-hexyl-1H-tetrazole (**27**).* White crystalline solid; mp 57–58 °C. ^{1}H NMR (500 MHz, acetone): δ 8.82–8.79 (3H, m), 4.89 (2H, s), 4.29 (2H, t, J=7.1 Hz), 1.81–1.76 (2H, m), 1.25–1.20 (6H, m), 0.82 (3H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, acetone): δ 149.28, 146.43, 144.77, 130.30, 118.25, 48.66, 31.67, 30.55, 30.32, 26.52, 22.96, 14.10. IR (KBr): 3111, 2933, 2859, 1541 (NO_2), 1460, 1426, 1385, 1343 (NO_2), 1179, 1074, 809, 729, 675 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_6O_4Se$: C, 40.69; H, 4.39; N, 20.33. Found: C, 41.01; H, 4.61; N, 20.14. LRMS m/z (ESI) 415.0 (100, MH^+), 413.1 (43), 416.9 (16%).

*4.6.7. 5-Methylselanyl-1-octyl-1H-tetrazole (**28**).* Yellowish viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23 (2H, t, J=7.2 Hz), 2.72 (3H,

s), 1.93–1.84 (2H, m), 1.35–1.22 (10H, m), 0.91–0.84 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.44, 47.99, 31.65, 29.19, 28.97, 28.82, 26.30, 22.57, 14.04, 8.14. IR (KBr): 2926, 2856, 2218, 1457, 1427, 1383, 1276, 1176, 1087, 975, 924, 724 cm^{-1}. LRMS *m*/*z* (ESI) 276.9 (100, MH^+), 274.8 (48), 273.9 (19%); HRMS *m*/*z* (ESI) calcd for $C_{10}H_{20}N_4Se+H^+$ ($M+H^+$) 277.09260, found 277.09263.

*4.6.8. 5-Benzylselanyl-1-octyl-1H-tetrazole (**29**).* Yellowish viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.22 (5H, m), 4.55 (2H, s), 4.07 (2H, t, *J*=7.3 Hz), 1.78–1.68 (2H, m), 1.31–1.16 (10H, m), 0.86 (3H, t, *J*=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.90, 136.71, 128.91, 128.80, 127.92, 47.94, 32.89, 31.61, 29.23, 28.91, 28.74, 26.21, 22.53, 14.01. IR (KBr): 2926, 2855, 1495, 1454, 1426, 1381, 1174, 760, 723, 697 cm^{-1}. LRMS *m*/*z* (ESI) 352.8 (100, MH^+), 350.9 (53), 354.8 (21%); HRMS *m*/*z* (ESI) calcd for $C_{16}H_{24}N_4Se+H^+$ ($M+H^+$) 353.12390, found 353.12386.

*4.6.9. 5-(3,5-Dinitrobenzylselanyl)-1-octyl-1H-tetrazole (**30**).* White solid; mp 61–62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (1H, t, *J*=2.1 Hz), 8.69 (2H, d, *J*=2.1 Hz), 4.76 (2H, s), 4.19 (2H, t, *J*=7.2 Hz), 1.88–1.76 (2H, m), 1.32–1.20 (10H, m), 0.90–0.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.54, 144.97, 142.05, 129.40, 118.12, 48.23, 31.59, 29.66, 29.23, 28.91, 28.75, 26.27, 22.53, 14.01. IR (KBr): 3087, 2930, 2857, 1533 (NO_2), 1450, 1430, 1344 (NO_2), 1175, 1084, 931, 809,732, 676 cm^{-1}. Anal. Calcd for $C_{16}H_{22}N_6O_4Se$: C, 43.54; H, 5.02; N, 19.04. Found: C, 43.58; H, 5.36; N, 19.07.

*4.6.10. 1-Cyclohexyl-5-methylselanyl-1H-tetrazole (**31**).* Yellowish viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20–4.07 (1H, m), 2.71 (3H, s), 2.10–1.87 (6H, m), 1.80–1.70 (1H, m), 1.54–1.19 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.42, 58.85, 32.21, 25.14, 24.78, 7.99. IR (KBr): 2935, 2857, 1452, 1423, 1383, 1366, 1272, 1189, 1083, 1001, 894, 817, 752 cm^{-1}. LRMS *m*/*z* (ESI) 246.9 (100, MH^+), 244.8 (52), 243.0 (20%); HRMS *m*/*z* (ESI) calcd for $C_8H_{14}N_4Se+H^+$ ($M+H^+$) 247.04564, found 247.04571.

*4.6.11. 5-Benzylselanyl-1-cyclohexyl-1H-tetrazole (**32**).* White solid; mp 62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.32–7.20 (5H, m), 4.53 (2H, s), 4.08–3.97 (1H, m), 1.90–1.79 (6H, m), 1.71–1.67 (1H, m), 1.37–1.20 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.91, 136.79, 128.91, 128.77, 127.83, 58.81, 32.77, 32.23, 25.08, 24.73. IR (KBr): 2935, 2857, 1494, 1452, 1421, 1365, 1272, 1185, 1083, 1001, 894, 817, 753, 696 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_4Se$: C, 52.34; H, 5.65; N, 17.44. Found: C, 52.27; H, 5.98; N, 17.36. LRMS *m*/*z* (ESI) 322.97 (100, MH^+), 321.0 (48), 319.01 (19%).

*4.6.12. 1-Cyclohexyl-5-(3,5-dinitrobenzylselanyl)-1H-tetrazole (**33**).* Yellowish crystalline solid; mp 103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.94–8.90 (1H, m), 8.72–8.69 (2H, m), 4.77 (2H, s), 4.13–4.04 (1H, m), 2.02–1.86 (6H, m), 1.77–1.74 (1H, m), 1.46–1.22 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.51, 143.93, 142.17, 129.44, 118.07, 59.27, 32.29, 29.48, 25.05, 24.67. IR (KBr): 3095, 2941, 2859, 1538 (NO_2), 1452, 1424, 1383, 1361, 1342 (NO_2), 1276, 1198, 1083, 1005, 922, 817, 808, 731, 671 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_6O_4Se$: C, 40.89; H, 3.92; N, 20.43. Found: C, 40.93; H, 4.21; N, 20.74.

*4.6.13. 1-Cyclohexyl-5-(2,4-dinitrobenzylselanyl)-1H-tetrazole (**34**).* Yellowish crystalline solid; mp 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (1H, d, *J*=2.3 Hz), 8.41 (1H, dd, *J*=8.6, 2.3 Hz), 8.18 (1H, d, *J*=8.6 Hz), 4.94 (2H, s), 4.07–3.98 (1H, m), 2.01–1.85 (6H, m), 1.78–1.71 (1H, m), 1.46–1.20 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.44, 146.94, 145.12, 141.32, 134.33, 128.21, 121.08, 59.20, 32.22, 28.08, 25.04, 24.68. IR (KBr): 3089, 2955, 2853, 1611, 1537 (NO_2), 1455, 1426, 1340 (NO_2), 1277, 1193, 1175, 1083, 997, 913, 817, 802, 744, 712, 684 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_6O_4Se$: C, 40.89; H, 3.92; N, 20.43. Found: C, 40.57; H, 4.17; N, 20.06.

Acknowledgements

This work was supported by the Grant Agency of Charles University (Project GAUK 55610/2010) and Charles University in Prague (SVV 267 001).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.07.103. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Schwarz, K.; Foltz, C. *J. Am. Chem. Soc.* **1957**, *79*, 3292–3293.
2. Dodig, S.; Cepelak, I. *Acta Pharm.* **2004**, *54*, 261–276.
3. Koketsu, M.; Ishihara, H. *Curr. Org. Chem.* **2003**, *7*, 175–185.
4. Libero, F. M.; Xavier, M. C. D.; Victoria, F. N.; Nascente, P. S.; Savegnago, L.; Perin, G.; Alves, D. *Tetrahedron Lett.* **2012**, *53*, 3091–3094.
5. Koketsu, M.; Tanaka, K.; Takenaka, Y.; Kwong, C. D.; Ishihara, H. *Eur. J. Pharm. Sci.* **2002**, *15*, 307–310.
6. Parnham, M. J.; Graf, E. *Prog. Drug Res.* **1991**, *36*, 9–47.
7. Koketsu, M.; Ishihara, H.; Wu, W. J.; Murakami, K.; Saiki, I. *Eur. J. Pharm. Sci.* **1999**, *9*, 157–161.
8. May, S. W.; Wang, L. Q.; GillWoznichak, M. M.; Browner, R. F.; Ogonowski, A. A.; Smith, J. B.; Pollock, S. H. *J. Pharm. Exp. Ther.* **1997**, *283*, 470–477.
9. Roh, J.; Vavrova, K.; Hrabalek, A. *Eur. J. Org. Chem.* **2012**, 6101–6118.
10. Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Khim. Geterotsikl. Soedin.* **2007**, 3–13.
11. Muraglia, E.; Kinzel, O. D.; Laufer, R.; Miller, M. D.; Moyer, G.; Munshi, V.; Orvieto, F.; Palumbi, M. C.; Pescatore, G.; Rowley, M.; Williarns, P. D.; Summa, V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2748–2752.
12. Adamec, J.; Waisser, K.; Kunes, J.; Kaustova, J. *Arch. Pharm.* **2005**, *338*, 385–389.
13. Adamec, J.; Beckert, R.; Weiss, D.; Klimesova, V.; Waisser, K.; Mollmann, U.; Kaustova, J.; Buchta, V. *Bioorg. Med. Chem.* **2007**, *15*, 2898–2906.
14. Shin, K. J.; Koo, K. D.; Yoo, K. H.; Kim, D. C.; Kim, D. J.; Park, S. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1421–1425.
15. Dhayanithi, V.; Syed, S. S.; Kumaran, K.; Sankar, K. R. J.; Ragavan, R. V.; Goud, P. S. K.; Kumari, N. S.; Pati, H. N. *J. Serb. Chem. Soc.* **2011**, *76*, 165–175.
16. Disli, A.; Salman, M. *Russ. J. Org. Chem.* **2009**, *45*, 151–153.
17. Sureshbabu, V. V.; Vasantha, B.; Hemantha, H. P. *Synthesis* **2011**, 1447–1455.
18. Kanakaraju, S.; Prasanna, B.; Chandramouli, G. V. P. *J. Chem. Pharm. Res.* **2012**, *4*, 2994–2998.
19. Koldobskii, G. I.; Kharbash, R. B. *Russ. J. Org. Chem.* **2003**, *39*, 453–470.
20. Yildirir, Y.; Us, M. F.; Colak, N.; Ozkan, H.; Yavuz, S.; Disli, A.; Ozturk, S.; Turker, L. *Med. Chem. Res.* **2009**, *18*, 91–97.
21. Bartelskeith, J. R.; Mahoney, J. B.; Puttick, A. J. *J. Org. Chem.* **1985**, *50*, 980–987.
22. Bartelskeith, J. R.; Burgess, M. T.; Stevenson, J. M. *J. Org. Chem.* **1977**, *42*, 3725–3731.
23. Kikuchi, S.; Endou, T.; Satou, K. JP52046817 (A), 1977.
24. Haniyu, T.; Ibe, Y. JP61147250 (A), Japan, 1986.
25. Barr, C. U.S. Patent 3,733,201 (A), 1973.
26. Kauer, J. C.; Sheppard, W. A. *J. Org. Chem.* **1967**, *32*, 3580–3592.
27. Lieber, E.; Ramachandran, J. *Can. J. Chem.* **1959**, *37*, 101–109.
28. Han, S. Y.; Lee, J. W.; Kim, H. J.; Kim, Y. J.; Lee, S. W.; Gyoung, Y. S. *Bull. Korean Chem. Soc.* **2012**, *33*, 55–59.
29. Fernandez-Bolanos, J. G.; Lopez, O.; Ulgar, V.; Maya, I.; Fuentes, J. *Tetrahedron Lett.* **2004**, *45*, 4081–4084.
30. Iwaoka, M.; Tomoda, S. *Top. Curr. Chem.* **2000**, *208*, 55–80.
31. Christophe, T.; Jackson, M.; Jeon, H. K.; Fenistein, D.; Contreras-Dominguez, M.; Kim, J.; Genovesio, A.; Carralot, J. P.; Ewann, F.; Kim, E. H.; Lee, S. Y.; Kang, S.; Seo, M. J.; Park, E. J.; Skovierova, H.; Pham, H.; Riccardi, G.; Nam, J. Y.; Marsollier, L.; Kempf, M.; Joly-Guillou, M. L.; Oh, T.; Shin, W. K.; No, Z.; Nehrbass, U.; Brosch, R.; Cole, S. T.; Brodin, P. *PLoS Pathog.* **2009**, *5*.
32. Makarov, V.; Manina, G.; Mikusova, K.; Mollmann, U.; Ryabova, O.; Saint-Joanis, B.; Dhar, N.; Pasca, M. R.; Buroni, S.; Lucarelli, A. P.; Milano, A.; De Rossi, E.; Belanova, M.; Bobovska, A.; Dianiskova, P.; Kordulakova, J.; Sala, C.; Fullam, E.; Schneider, P.; McKinney, J. D.; Brodin, P.; Christophe, T.; Waddell, S.; Butcher, P.; Albrethsen, J.; Rosenkrands, I.; Brosch, R.; Nandi, V.; Bharath, S.; Gaonkar, S.; Shandil, R. K.; Balasubramanian, V.; Balganesh, T.; Tyagi, S.; Grosset, J.; Riccardi, G.; Cole, S. T. *Science* **2009**, *324*, 801–804.
33. Trefzer, C.; S'Kovierova, H.; Buroni, S.; Bobovska, A.; Nenci, S.; Molteni, E.; Pojer, F.; Pasca, M. R.; Makarov, V.; Cole, S. T.; Riccardi, G.; Mikusova, K.; Johnsson, K. *J. Am. Chem. Soc.* **2012**, *134*, 912–915.

34. Koci, J.; Klimesova, V.; Waisser, K.; Kaustova, J.; Dahse, H. M.; Mollmann, U. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3275–3278.
35. Sommen, G. L.; Linden, A.; Heimgartner, H. *Eur. J. Org. Chem.* **2005**, 3128–3137.
36. Fleischhauer, J.; Beckert, R.; Gunther, W.; Kluge, S.; Zahn, S.; Weston, J.; Berg, D.; Gorls, H. *Synthesis* **2007**, 2839–2848.
37. Atanassov, P. K.; Linden, A.; Heimgartner, H. *Heterocycles* **2003**, *61*, 569–579.
38. Kaname, M.; Minoura, M.; Sashida, H. *Tetrahedron Lett.* **2011**, *52*, 505–508.
39. Zhou, Y. H.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2000**, *83*, 1576–1598.
40. Koketsu, M.; Kogami, M.; Ando, H.; Ishihara, H. *Synthesis* **2006**, 31–36.
41. Atanassov, P. K.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2010**, *93*, 395–404.
42. Fleischhauer, J.; Beckert, R.; Hornig, D.; Gunther, W.; Gorls, H.; Klimesova, V. *Z. Naturforsch., B* **2008**, *63*, 415–424.
43. Sashida, H.; Pan, C.; Kaname, M.; Minoura, M. *Synthesis* **2010**, 3091–3096.
44. Kanoh, K.; Ishihara, H.; Koketsu, M. *Synthesis* **2007**, 2617–2620.
45. Atanassov, P. K.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2003**, *86*, 3235–3243.
46. Koketsu, M.; Otsuka, T.; Ishihara, H. *Heterocycles* **2006**, *68*, 2107–2112.
47. Koketsu, M.; Yamamura, Y.; Ando, H.; Ishihara, H. *Heterocycles* **2006**, *68*, 1267–1273.
48. Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307–326.
49. Coppens, P. In *Crystallographic Computing*; Ahmed, F. R., Hall, S. R., Huber, C. P., Eds.; Munksgaard: Copenhagen, Denmark, 1970.
50. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1994**, *27*, 1045–1050.
51. Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Göttingen, Germany.
52. Koketsu, M.; Takahashi, A.; Ishihara, H. *J. Heterocycl. Chem.* **2007**, *44*, 79–81.
53. Henriksen, L.; Ehrbar, U. *Synthesis* **1976**, 519–521.
54. Maeda, H.; Takashima, M.; Sakata, K.; Watanabe, T.; Honda, M.; Segi, M. *Tetrahedron Lett.* **2011**, *52*, 415–417.
55. Collard-Charon, C.; Huls, R.; Renson, M. *Bull. Soc. Chim. Belg.* **1962**, *71*, 541–553.
56. Lopez, O.; Maza, S.; Ulgar, V.; Maya, I.; Fernandez-Bolanos, J. G. *Tetrahedron* **2009**, *65*, 2556–2566.
57. Boyer, J. H.; Frints, P. J. A. *Tetrahedron Lett.* **1968**, *9*, 3211–3212.