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EFFICIENT SYNTHESIS OF NOVEL DIORGANYL SELENIDES VIA CLEAVAGE OF SE–SE BOND OF DISELENIDES BY $RUCL_3$/ZN AND SCREENED FOR THEIR BIOLOGICAL EFFICACY

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ABSTRACT

The $RuCl_3$-catalysed cross-coupling reaction of novel diorganyl diselenides with benzyl halides using Zinc as an additive. This cross-coupling reaction was performed with amide conjugated diaryl diselenides with benzyl halides bearing electron-withdrawing and electron-donating groups, affording corresponding diaryl selenides in good yield and further characterized by using Mass, ^{1}H NMR, ^{13}C NMR, ^{77}Se NMR and elemental analysis. The title compounds were evaluated for their *in vitro* Antioxidant and Antibacterial activity.

KEYWORDS: Diselenides, $RuCl_3$/Zn cleavage, Diorganyl Selenides, Organoselenium compounds, Antioxidant activity, Antibacterial activity.

INTRODUCTION

Organic selenides have been used as versatile reagents in organic synthesis and catalysis.[1] Chalcogens, especially with selenium and tellurium as structural motifs, are generally found in a variety of biological and pharmaceutical molecules[2] and in materials science.[3] Additionally, organoselenium compounds have emerged as an exceptional class of structures that exemplify a role in biochemical processes, serving as important therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements.[4] To synthesize these compounds, a number of synthetic methods have been explored.[5]

Organoselenium compounds have found such wide utility because of their effects on an extraordinary number of very different reactions, including many asymmetric

transformations.[6] Furthermore, organoselenium compounds have been attracting considerable attention, especially for their biological and medicinal properties, due to their ability to mimic natural compounds with important biological properties (*e.g.*, antitumor, anti-inflammatory, antioxidant and anti-infective activities).[7] Investigation of synthetic methods for the preparation of selenocysteine,[8] selenium-based peptides,[9] selenoglycosides[10] and other important natural compounds[11] is nowadays an area of intensive research.

The development of new methods for the introduction of selenium-containing groups into organic molecules remains a significant challenge,[12] specially the preparation of unsymmetrical diorganyl selenides.[13] In general, to avoid handling unstable reagents, such as selenols, diorganyl diselenides are used as starting materials and the selenium anion is generated in situ via chemical Se–Se bonds reduction. However, this procedure often requires drastic reaction conditions, such as reduction with hydrides,[14] which reduces the possibility of some functionality or more complex substrates to be present.

Recently, a $Zn/AlCl_3$ system was employed to synthesize selenol esters by the reactions of diphenyl and dibenzyl diselenides with acid chlorides.[15a] A modified $Zn/AlCl_3$ system was applied for preparation of unsymmetrical diorganyl selenides from the reactions of dibenzyl diselenide with reactive bromides, i.e., benzyl bromide and ethyl R-bromoacetate, in moderate yields.[15b] Cleavage of Se-Se bonds in diaryl diselenides has received more attention than that of dialkyl diselenides in the literature because diaryl diselenides are more reactive and only a few examples involving reactions of dialkyl diselenides with reactive organic bromides were reported.[16]

Taking into account these constraints, we were motivated to investigate the synthesis of new kind of diselenides and development of efficient catalytic procedures to cleave these diorganyl diselenides to unsymmetrical benzylselenides was one of our goals. Herein, we report the ruthenium (III) chloride catalyzed synthesis of unsymmetrical diorganyl selenides from the reactions of 2,2'-diselanediylbis(*N*-phenylacetamide) with benzyl halides in the presence of zinc.[17] To the best of our knowledge, synthesis and catalytic reactions of 2,2'-diselanediylbis(*N*-phenylacetamide) with organic halides have never been reported.

MATERIALS AND METHODS

All reagents and solvents were purchased from Merck (Darmstadt, Germany) chemical AR grade and were used as provided. DPPH and BHA were purchased from Sigma-Aldrich chemical Co. (St. Louis, MO, USA). TLC analysis was performed on alumina sheets precoated with silica gel 60F-254 and SiO_2, 200-400 mesh (Merck) was used for column chromatography. ^{1}H (400 MHz), ^{13}C (100.56 MHz) and ^{77}Se (76.29 MHz) NMR spectra were obtained on a Bruker 400 MHz NMR spectrometer. Chemical shifts are cited with respect to $SiMe_4$ as internal (^{1}H and ^{13}C) and Me_2Se as external (^{77}Se) standards. Mass spectral studies were carried out on a Bruker Daltonics 6000 plus mass spectrometer with ESI-MS mode analysis.

General procedure

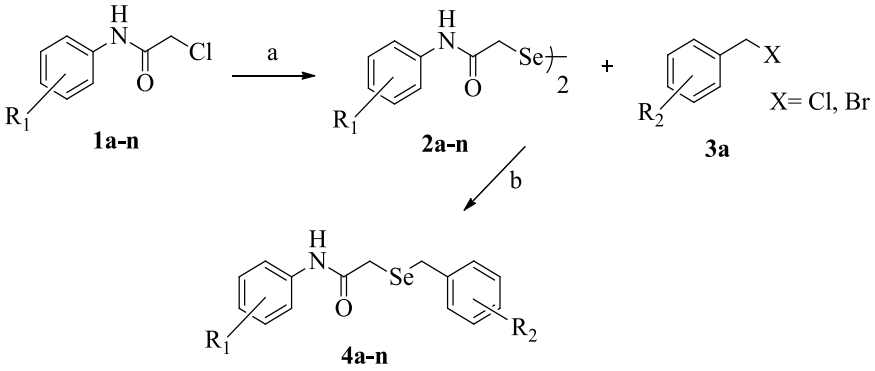
Preparation of 2,2'-diselanediylbis(N-phenylacetamide)2a-n

A flame-dried round bottom flask was charged with different aniline derivatives **(1a-n)** (1.0 mmol) in dry methylene chloride (2 mL) and triethylamine (2.2 mmol). The mixture was cooled on ice for 10 min. Through a dropping funnel, a solution of 2-chloroacetyl chloride (1.1 mmol) in DCM (2 mL) was added over a period of 10 min. The mixture was allowed to warm up to room temperature and stirring was continued for reaction completion. The mixture was poured into water and the organic layer was separated, dried over $MgSO_4$, filtered, and evaporated to give crude products. Crude product was purified over a silica gel column using methylene chloride as an eluant to give chloro amide **1a-n**. Elemental selenium (2.0mmol) was suspended in ethanol and cooled to $0^{o}C$ followed by the addition of $NaBH_4$ (1.5mmol) and stirred for 10mins and 2-chloro-*N*-phenylacetamide (**1a-n**) (1.0mmol) was charged. The reaction mixture was stirred at rt to obtain 2,2'-diselanediylbis(*N*-phenylacetamide) analogues. After completion of the reaction confirmed by TLC, evaporate the solvent and extracted to ethylacetate and wash thoroughly with water to get crude product. Crude product was purified over a silica gel column using $CHCl_3$: MeOH system to give 2,2'-diselanediylbis(*N*-phenylacetamide)**2a-n**.

Preparation of 2-(benzylselanyl)-N-phenylacetamide 4a-n

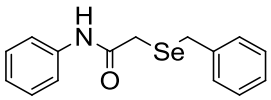
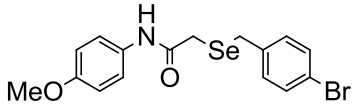
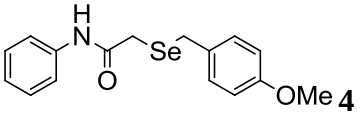
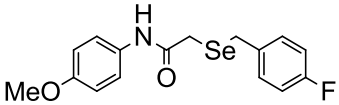
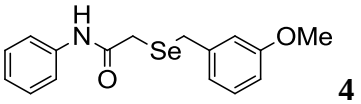
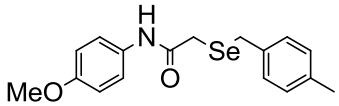
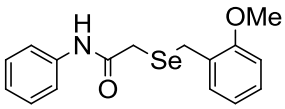
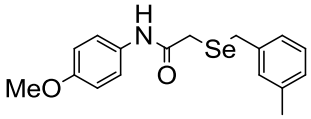
Under nitrogen atmosphere, to a mixture of 2,2'-diselanediylbis(*N*-phenylacetamide) (2a-n) (0.5 mmol), zinc (20mol%) and ruthenium(III) chloride hydrate (2mol%) were successively added DMF (3 mL) and benzyl halides (**3a**)(1.2 mmol). The mixture was stirred at 90°C for 1 h. After the mixture was cooled to ambient temperature, 10 mL of water was added, and the

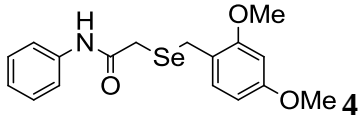
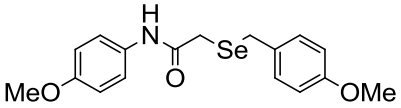
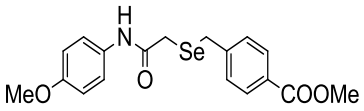
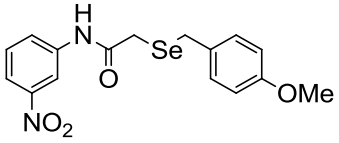
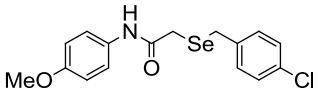
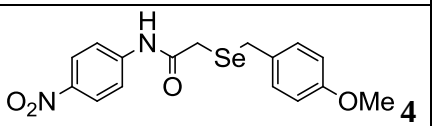
resultant mixture was extracted with diethyl ether (3 X 20 mL). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$ and filtered through Celite. All volatiles were removed under reduced pressure and crude product was purified over a silica gel column using $CHCl_3$: MeOH system to give titled compounds (Table 1) (Scheme 1). The products were further characterized. Selected data; *2-(benzylselanyl)-N-phenylacetamide (4a)*, Pale yellow semi solid, yield 93%, ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H, NH), 7.48-6.77 (m, 10H, Ar-H), 3.88 (s, 2H, CH_2), 3.56 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.15, 139.06, 136.51, 128.76, 128.28, 126.63, 119.97, 114.55, 38.63, 33.13. ^{77}Se NMR ($CDCl_3$, Me_2Se) δ (ppm): 212; HRMS (ESI mode) calcd. For $C_{15}H_{15}NOSe$ (M+Na) 327.23, found 327.32. Elemental Analysis: calcd.; C, 59.22; H, 4.97; N, 4.60; Se, 25.95, found; C, 59.18; H, 4.95; N, 4.60; se, 25.96.



Scheme 1. Preparation of 2-(benzylselanyl)-*N*-phenylacetamide (4a-n). a) Se, $NaBH_4$, EtOH, r.t., 1hr; b) 2mol% $RuCl_3$, 20mol% Zn, DMF, 90^{o}C, 1hr.

Table 1. List of synthesized monoselenides.

Sl. No.	Product 4a-n	Sl.No	Product 4a-n
1	 **4a**	8	 **4h**
2	 **4b**	9	 **4i**
3	 **4c**	10	 **4j**
4		11	

	4d		4k
5	 **4e**	12	 **4l**
6	 **4f**	13	 **4m**
7	 **4g**	14	 **n**

Antioxidant studies

DPPH free radical scavenging assay

The evaluation of antioxidant activity of newly synthesized compounds was done by DPPH radical scavenging activity assay.[18] Internal standard BHA and the synthesized compounds of different concentrations were prepared in distilled ethanol, 1 mL of each compound solutions having different concentrations (10 µM, 25 µM, 50 µm, 100 µM, 200 µM and 500 µM) were taken in different test tubes 4 mL of 0.1 mM ethanol solution of DPPH was added and shaken vigorously. The tubes were then incubated in the dark room at RT for 20 min. A DPPH blank was prepared without compound and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV-visible spectrophotometer and the remaining DPPH was calculated. The percent decrease in the absorbance was recorded for each concentration and percent quenching of DPPH was calculated on the basis of the observed decreased in absorbance of the radical. The radical scavenging activity was expressed as the inhibition percentage and was calculated using the formula.

$$\text{Radical scavenging activity (\%)} = [(A_o - A_1)/A_o \text{ X } 100].$$

Where A_o is the absorbance of the control (blank, without compound) and A_1 is the absorbance of the compound.

Inhibition of microsomal lipid peroxidation assay

Liver excised from adult male Wister rats, were homogenized with a polytron (speed setting 7-8) in 10 mL of ice cold Tris-HCl buffer (20 mM, pH 7.4) by following literature method.[19] The homogenate was centrifuged at 14000 rpm for 15 min. The supernatants (1 mL) were

incubated with different concentration of compounds (10-500 µM) in the presence of 10 µM $FeSO_4$ and 0.1 mM ascorbic acid at 37°C for 1 hr. The reaction was terminated by the addition of 1.0 mL of trichloroacitic acid (TCA; 28%) and 1.5 mL of thiobarbituric acid (TBA; 1%). The solution was heated at 100°C for 15 min, cooled to room temperature, and centrifuged at 2500 rpm for 15 min, and the color of the MDA-TBA complex in the supernatant was read at 532 nm using a spectrophotometer. Butylated hydroxy anisole was used as a positive control. The inhibition ratio (%) was calculated using the following formula: inhibition ratio (%) = $(A - A_1)/A$ X 100, where A is the absorbance of the control and A_1 is the absorbance of the test sample.

Antibacterial activity

In vitro antibacterial activity was evaluated against Ralstonia solanacearum, Escherichia coli, *Klebsiella pneumonia, Lactobacillus, Bacillus subtilis* by agar well diffusion method.[20]

The microorganisms were inoculated in to the sterilized nutrient broth and maintained at 37°C for 24 h. On the day of testing, bacteria were subcultured separately into 25 mL of sterilized nutrient broth. Inoculated subcultured broths were kept at room temperature for the growth of inoculums. Each test compound (**4a-m**) and standard drug of 10 mg was dissolved in 10 mL of DMSO to get a concentration of 1 µg/mL and further diluted to get a final concentration of 50 µg/mL. About 15-20 mL of molten nutrient agar was poured into each of the sterile plates. With the help of cork borer of 6mm diameter, the cups were punched and scooped out of the set agar and the plates were inoculated with the suspension of particular organism by spread plate technique. The cups of inoculated plates were then filled with 0.1 mL of the test solution, Chloromphenicol solution and DMSO (negative control). The plates were allowed to stay for 24 h at 37°C and zone of inhibition (mm) was then measured.

RESULT AND DISCUSSION

Chemistry

In the present work, we have demonstrated that the 2,2'-diselanediylbis(*N*-phenylacetamide) can be readily synthesized from 2-chloro-N-phenylacetamide followed by treatment with benzyl halides give 2-(benzylselanyl)-*N*-phenylacetamide in the presence of $Zn/RuCl_3$. The products were further characterized. The peak around 8.5ppm in the ^1H NMR spectrum of **4a-n** indicates the presence of the –NH group. The peaks of corresponding $–CH_2$ protons shifted slightly downfield due to conjugation of amide and selenium. The ^{77}Se NMR spectra for all

the compounds were recorded in $CDCl_3$ solution. There is a large upfield shift for products (ppm) compared to the precursor diselenide (ppm) indicates the formation of monoselenide.

Biological efficacy

Antioxidant activity

Evaluation of antioxidant activity for the newly synthesized analogues was done by using two in vitro assays such as 2,2-diphenyl- 1-picryl-hydrazyl (DPPH) radical scavenging activity and inhibition microsomal lipid peroxidation (LPO). The antioxidant properties were expressed as 50% inhibitory concentration (IC50) values (Table 2). The DPPH radical scavenging evaluation is a standard assay in antioxidant activity studies and offers a rapid technique for screening the radical scavenging activity (RSA) of specific compounds. The reaction of synthesized compounds with stable DPPH free radical indicates their free radical scavenging ability.

Majority of the tested compounds in these series (**4a–m**) showed good to high activity. Dominant RSA was observed, this may be presence of Selenium moiety adjacent to amide group in the skeleton. When compared to standard. Antioxidant activity of these compounds is related with their electron- or hydrogen-donating ability to DPPH radical, so that it become stable diamagnetic molecules. This might be the reason for the higher antioxidant activity of the compounds **4b**,**4d**,**4e**,**4f**, and **4l** among the synthesize analogues. The marginal decrease in the activity of **4g**, **4h**, **4j** and **4m** is due to introduction of electron withdrawing (Br, Cl, NO_2 and F) substituents to phenyl group.

Table 2. 50% Inhibition of DPPH radical and microsomal LPO inhibition by compounds (4a–m).Each value represents mean ± SD (n = 3)

Compounds No.	DPPH activity IC_{50}[a] µM/ml	LPO inhibition IC_{50}[b] µM/ml
4a	20 ± 0.23	23± 0.75
4b	13± 0.10	15 ± 0.76
4c	23± 0.81	16± 0.43
4d	12± 0.11	14 ± 0.19
4e	12± 0.72	13± 0.25
4f	13± 0.35	14± 0.21
4g	18± 0.64	22± 0.14
4h	15± 0.71	16± 0.42
4j	16± 0.43	19± 0.19
4l	13± 0.27	13± 0.91
4m	18± 0.23	17± 0.20
BHA	12± 0.21	14± 0.14

[a] IC50 = the concentration (µM/mL) exhibiting 50% inhibition of DPPH radical.

[b] IC50 = the concentration (µM/mL) exhibiting 50% inhibition of LPO oxidation.

Inhibition of lipid peroxidation property of newly synthesized compounds was performed by the formation of thiobarbutaric acid reactive species (TBARS) using liver excised from adult male Wister rats. Lipid free radicals produced by ferric chloride and vitamin C rapidly react with oxygen molecule to give peroxy radicals with the subsequent formation of the final product, malondialdehyde. The results showed that all newly synthesized compounds (**4a–m**) inhibited the ferric chloride induced lipid peroxidation and varying degree compared with standard antioxidant BHA Table 2. Compound **4e** which contains two -OCH_3 and compound **4f** having -COOMe and -OCH_3 group at phenyl ring showed maximum inhibition and even higher than that of the reference compound BHA. In general, the presence of electron-donating groups on the phenyl ring favors the activity. This might be the reason for the four-six times enhancement of activity of the other compounds, which showed good to high activities in the order **4e > 4l > 4f > 4d > 4b > 4c** which has free methoxy and methyl as the electron donating substituent's. The presence of electron withdrawing groups on the phenyl ring was not favor for the activity, thus might be the reason for the decreased activity for the compounds **4g**, **4h** and **4i**.

Antibacterial activity

The antibacterial activities of newly synthesized compounds (**4a–m**) were determined by well plate method. In this work, *Ralstonia solanacearum, Escherichia coli, Klebsiella pneumonia, Lactobacillus, Bacillus subtilis* were used to investigate the activity. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at concentrations of 1 and 0.5 mg/mL. The antibacterial screening revealed that some of the tested compounds showed good inhibition against various tested microbial strains Table 3. Compounds **4a**, **4b**, **4j** and **4l** possessed least antibacterial activity may be due to presence of electron withdrawing groups. Further replacement of substituents with electron donating groups (Cl, Br, F and NO_2) increases the activity and which is higher than that of standard compounds, and order will be given as **4g** > **4h** > **4m** > **4l**.

Table 3. Antibacterial activity of the compounds (4a–m). Inhibitory zone (diameter) mm of the synthesized compounds against tested bacterial strains by well plate method.

Sl. No Compound	*Ralstonia solanacearum*	*Escherichia coli*	*Klebsiella pneumoniae*	*Lactobacillus*	*Bacillus subtilis*
4a	9±0.10	8±0.19	8±0.11	6±0.25	4±0.15
4b	9±0.18	7±0.24	5±0.12	4±0.09	3±0.22
4c	11±0.10	3±0.29	2±0.10	6±0.10	6±0.11
4d	10±0.15	11±0.28	09±0.15	11±0.15	8±0.01
4e	8 ±0.11	11±0.13	12±0.13	6±0.16	8±0.13
4f	11±0.18	10±0.28	13±0.13	9±0.26	8±0.09
4g	18±0.10	16±0.27	13±0.14	12±0.21	16±0.13
4h	16±0.26	19±0.14	15±0.14	17±0.18	12±0.21
4j	9±0.37	9±0.27	8±0.15	3±0.10	4±0.28
4l	7±0.24	6±0.17	6±0.25	4±0.10	4±0.1
4m	14±0.12	17±0.27	13±0.16	11±0.15	18±0.10
Standard Chloromphenocal	12±0.11	14±0.20	12±0.29	10±0.14	10±0.15

CONCLUSION

In the present study, we have described efficient synthesis of 2-(benzylselanyl)-*N*-phenylacetamide by cross-coupling reactions of diaryl diselenides with benzyl halides using $RuCl_3$/Zn as an efficient catalyst. The newly synthesized analogues were evaluated for their in vitro antioxidant and antimicrobial activity. Among the analogues compounds **4e** and **4l** demonstrated potent antioxidant activity. While, compounds **4g** and **4h** exhibited maximum antibacterial activity.

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