

Synthesis and characterization of 5-(2-nitro-1-arylpropyl)-4-aryl-1,2,3-selenadiazoles

S Saravanan[#], A Amuthavalli & S Muthusubramanian*

School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India

E-mail: muthumanian2001@yahoo.com

Received 11 February 2008; accepted (revised) 30 April 2009

The synthesis and characterization of new 5-(2-nitro-1-arylpropyl)-4-aryl-1,2,3-selenadiazoles, obtained from the α -functionalised semicarbazones are described. The structures of these compounds have been established by ^1H and ^{13}C NMR spectral data.

Keywords: 2-[4-Nitro-1,3-diarylpentylidene]-1-hydrazinecarboxamide, 1,2,3-selenadiazoles, ^1H NMR, ^{13}C NMR, mass spectrum

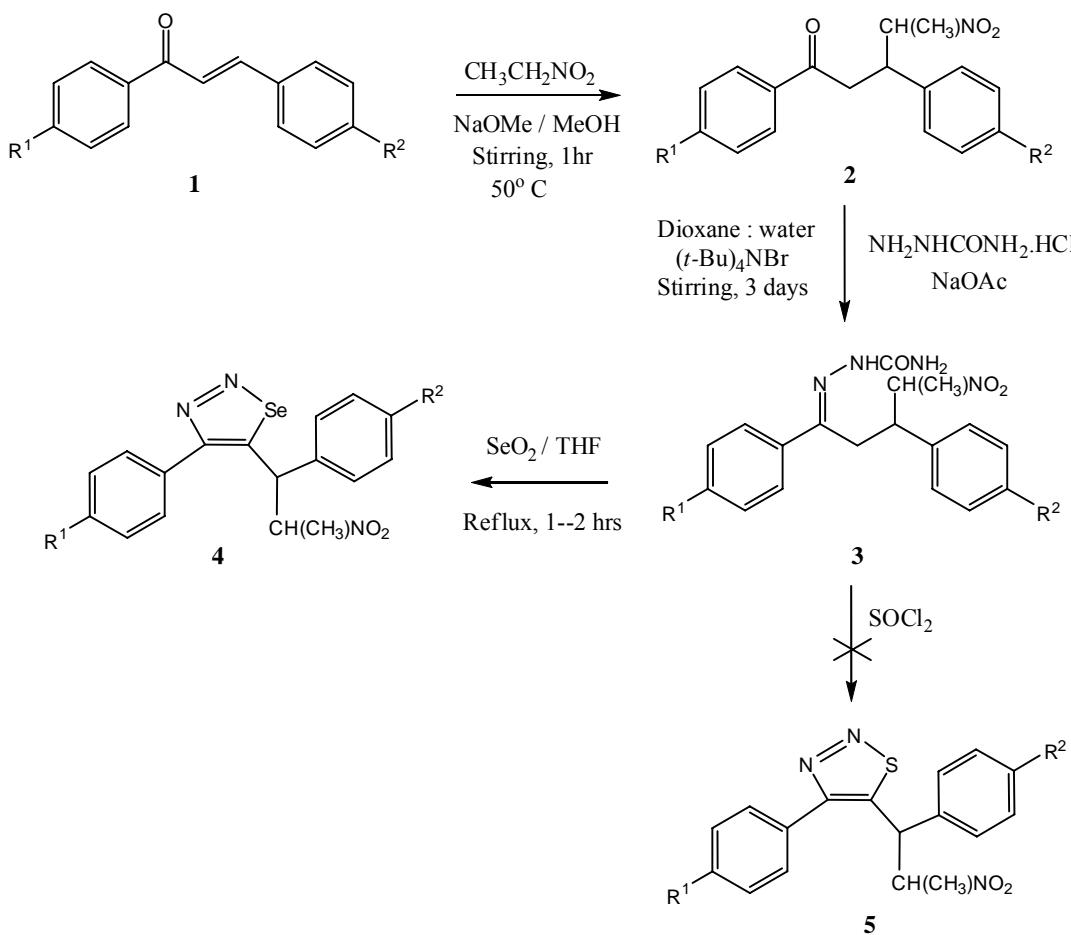
It has been reported that certain alkyl nitro compounds exhibit antitumour activity^{1,2}. Nitroalkanes have a detrimental effect on insects and on the growth of fungi^{3,4}. It has been reported that the nitro compounds possess antibacterial⁵ and rodent-repelling⁶ characteristics. Different side chain substituted selenadiazoles have been reported from our laboratory⁷, including a nitro substituted system^{7c}. This article describes the synthesis of another set of nitro substituted selenadiazoles and the target selenadiazoles can be further transformed *via* the active nitro group with the scope for building additional heterocyclic units. Selenadiazoles with nitro group may also possess significant biological activity and hence the target molecules assume importance.

The precursors for the selenadiazoles, the semicarbazones of ketones with active methylenes, have been synthesized by the conjugate addition of nitroethane to differently substituted benzylidene-acetophenones **1** in the presence of sodium methoxide. The addition has been carried out under mild condition giving moderate yields of the adducts. Interestingly, the addition has led to two diastereomers of **2** (**Scheme I**) with varying composition of the individual isomers. The ratio of the isomers is very much predictable from the intensity of the methyl doublets appearing around δ 1.50 and 1.35 ppm.

There is no uniformity in the ratio of the diastereomers and thus in the case of 1-(4-chlorophenyl)-4-nitro-3-phenyl-1-pentanone, **2d**, that diastereomer with downfield methyl doublet is dominant with 80% contribution, while in the case of 3-(4-methoxy-phenyl)-4-nitro-1-phenyl-1-pentanone, **2c**, the diastereomer with upfield methyl signal is dominant (70%). The two diastereomers of **2** have close R_f values and the attempts to separate them through chromatography technique did not yield the expected results. Thus though the formation of a mixture of diastereomeric ketones **2** is very much evident from ^1H and ^{13}C NMR spectra, their isolation is found to be difficult. The hydrogens attached to the chiral centers and the diastereotopic hydrogens of the methylene group of both the diastereomers appear in between δ 3.2 and 3.9 ppm as a complex pattern.

As the diastereoisomeric ketones could not be separated, further transformations have been carried out on this mixture in the hope of separating the isomers at a later stage. The second step in the proposed sequence is the conversion of the ketones to the respective semicarbazones. The conventional method of preparing the semicarbazones has not yielded appreciable amount of the product due to a competitive retro Michael reaction. Hence the semicarbazone formation has been effected under phase transfer condition using *t*-butylammonium bromide as the catalyst in dioxane and water. Quantitative conversion to the diastereomeric semicarbazones has been noticed from NMR spectra.

[#] Present Address: Department of Chemistry, A.N.J.A.College, Sivakasi



Entry	R ₁	R ₂
a	H	H
b	H	CH ₃
c	H	OCH ₃
d	Cl	H
e	Cl	Cl
f	CH ₃	OCH ₃

Scheme I

Though the separation of the diastereomeric ketones has been found to be difficult, the major isomer of the semicarbazone **3** has been separated through crystallization in ethanol. The data presented in **Table I** is that for the crystallized major diastereomer.

The crucial step involved in the synthesis of the target molecule is the oxidative cyclisation of the semicarbazone by selenium dioxide. The reaction has been carried out under different condition with different solvent and it has been found that tetrahydrofuran is a good medium for the conversion of semicarbazone to selenadiazole. Moderate to good yield of selenadiazoles (35-50%, **Table I**) has been achieved. The reaction has been carried out on the

major diastereomer of the semicarbazone and the product formed is a mixture of the selenadiazole **4** (**Scheme I**) and a small fraction of the parent ketone probably got hydrolyzed from the semicarbazones during the reaction. The yield, physical constant and the spectral data for **4** are provided in **Table I**.

The complete structural analysis for a representative selenadiazole **4e** achieved by a combination of 1D and 2D NMR spectroscopy is discussed here. A doublet with a coupling constant of 6.3 Hz accounting for three hydrogens appears at δ 1.42. There is a one hydrogen doublet with a coupling of 10.8 Hz at δ 4.92 with another one hydrogen signal at δ 4.97 as a quartet of doublet with coupling constants 10.8 and

Table I—Yield, physical constant and NMR data for **3** and **4**

Compd	Yield (%)	m.p. (°C)	¹ H NMR (ppm)	¹³ C NMR (ppm)
3a	75	94	1.68 (d, <i>J</i> = 6.6 Hz, 3H), 3.16-3.24 (m, 1H), 3.56-3.66 (m, 2H), 5.05-5.17 (m, 1H), 6.11 (bs, 2H), 7.03-7.07 (m, 2H), 7.13-7.16 (m, 3H), 7.33-7.35 (m, 3H), 7.39-7.43 (m, 2H), 9.74 (s, 1H)	18.7, 29.6, 48.1, 88.3, 127.4, 128.6, 128.8, 129.2, 129.3, 129.7, 133.5, 137.4, 146.5, 158.3
3b	81	110	1.29 (d, <i>J</i> = 6.6 Hz, 3H), 2.26 (s, 3H), 2.84-2.97 (m, 1H), 3.29-3.45 (m, 2H), 4.96-5.06 (m, 1H), 5.39 (bs, 1H), 6.02 (bs, 1H), 6.91 (d, <i>J</i> = 8.1 Hz, 2H), 7.02 (d, <i>J</i> = 8.1 Hz, 2H), 7.33-7.42 (m, 5H), 9.15 (s, 1H)	18.5, 20.9, 30.2, 46.9, 87.4, 126.4, 127.8, 128.4, 128.9, 129.6, 133.4, 136.9, 137.8, 146.6, 158.1
3c	65	74	1.29 (d, <i>J</i> = 6.6 Hz, 3H), 2.83-3.00 (m, 1H), 3.15-3.45 (m, 2H), 3.66 (s, 3H), 4.94-5.04 (m, 1H), 5.39 (bs, 1H), 6.05 (bs, 1H), 6.70 (d, <i>J</i> = 8.7 Hz, 2H), 7.32-7.42 (m, 7H), 9.69 (s, 1H)	18.5, 30.2, 46.6, 55.1, 87.6, 113.9, 126.4, 128.8, 129.0, 129.3, 136.9, 146.8, 147.9, 156.8, 159.1
3d	75	154	1.29 (d, <i>J</i> = 6.6 Hz, 3H), 2.92-2.97 (m, 1H), 3.38-3.52 (m, 2H), 4.99-5.09 (m, 1H), 5.34 (bs, 1H), 6.09 (bs, 1H), 6.98 (d, <i>J</i> = 8.4 Hz, 2H), 7.18 (d, <i>J</i> = 8.4 Hz, 2H), 7.37 (s, 5H), 9.79 (s, 1H)	18.5, 29.7, 46.7, 87.1, 126.4, 128.5, 128.9, 129.1, 129.6, 133.8, 135.0, 136.9, 146.6, 158.4
3e	72	173	1.28 (d, <i>J</i> = 6.6 Hz, 3H), 2.85 (dd, <i>J</i> = 14.4, 4.8 Hz, 1H), 3.48-3.57 (m, 2H), 5.01-5.11 (m, 1H), 5.98 (bs, 2H), 7.13 (d, <i>J</i> = 8.4 Hz, 2H), 7.19 (d, <i>J</i> = 8.4 Hz, 2H), 7.29-7.41 (m, 4H), 9.93 (s, 1H)	17.1, 27.7, 46.1, 86.3, 127.2, 128.2, 129.1, 132.8, 134.0, 134.4, 135.5, 143.7, 144.4, 157.6
3f	80	152	1.29 (d, <i>J</i> = 6.6 Hz, 3H), 2.38 (s, 3H), 2.85 (dd, <i>J</i> = 13.2, 10.2 Hz, 1H), 3.17-3.39 (m, 2H), 3.73 (s, 3H), 4.94-5.04 (m, 1H), 5.26 (bs, 1H), 6.06 (bs, 1H), 6.73 (d, <i>J</i> = 8.7 Hz, 2H), 7.15-7.19 (m, 4H), 7.30 (d, <i>J</i> = 8.1 Hz, 2H), 8.99 (s, 1H)	17.5, 21.2, 29.1, 46.6, 55.1, 87.1, 114.3, 128.9, 129.0, 129.1, 129.3, 134.1, 134.2, 144.8, 158.3, 159.2
4a	50	85	1.45 (d, <i>J</i> = 6.3 Hz, 3H), 5.05 (d, <i>J</i> = 10.5 Hz, 1H), 5.06 (qd, <i>J</i> = 10.5, 6.3 Hz, 1H), 7.22 (d, <i>J</i> = 8.1 Hz, 2H), 7.27-7.37 (m, 3H), 7.60 (s, 5H)	18.7, 50.6, 89.0, 127.6, 128.6, 129.2, 129.6, 130.0*, 131.2, 137.4, 158.8, 161.2
4b	40	-- [#]	1.43 (d, <i>J</i> = 6.3 Hz, 3H), 2.29 (s, 3H), 4.92-5.17 (m, 2H), 6.98 (d, <i>J</i> = 8.1 Hz, 2H), 7.12 (d, <i>J</i> = 8.1 Hz, 2H), 7.59 (s, 5H)	18.7, 21.0, 50.3, 89.2, 127.4, 128.8, 129.1, 129.7, 129.9, 130.2, 133.2, 138.4, 159.0, 160.8
4c	35	-- [#]	1.43 (d, <i>J</i> = 6.3 Hz, 3H), 3.76 (s, 3H), 4.91-5.15 (m, 2H), 6.85 (d, <i>J</i> = 8.7 Hz, 2H), 7.00 (d, <i>J</i> = 8.7 Hz, 2H), 7.54 (s, 5H)	18.6, 49.9, 55.2, 89.3, 114.8, 127.9, 128.7, 129.1, 129.2, 129.3, 129.5, 159.5, 159.6, 160.7
4d	39	82	1.41 (d, <i>J</i> = 5.7 Hz, 3H), 4.96-5.15 (m, 2H), 7.00 (d, <i>J</i> = 8.4 Hz, 2H), 7.13 (d, <i>J</i> = 8.4 Hz, 2H), 7.48-7.61 (m, 5H)	19.1, 50.5, 89.4, 129.4, 129.8, 130.1, 130.3*, 131.5, 134.9, 136.0, 158.5, 158.9
4e	44	125	1.42 (d, <i>J</i> = 6.3 Hz, 3H), 4.92 (d, <i>J</i> = 10.8 Hz, 1H), 4.97 (qd, <i>J</i> = 10.8, 6.3 Hz, 1H), 7.02 (d, <i>J</i> = 8.4 Hz, 2H), 7.34 (d, <i>J</i> = 8.4 Hz, 2H), 7.45 (d, <i>J</i> = 8.4 Hz, 2H), 7.55 (d, <i>J</i> = 8.4 Hz, 2H)	19.1, 50.3, 90.6, 129.3, 129.5, 129.7, 130.0, 131.2, 134.3, 134.8, 135.7, 158.9, 159.2
4f	46	114	1.43 (d, <i>J</i> = 6.3 Hz, 3H), 2.48 (s, 3H), 3.77 (s, 3H), 4.91-5.14 (m, 2H), 6.84 (d, <i>J</i> = 8.1 Hz, 2H), 7.02 (d, <i>J</i> = 8.7 Hz, 2H), 7.12 (d, <i>J</i> = 8.7 Hz, 2H), 7.48 (d, <i>J</i> = 8.1 Hz, 2H)	19.1, 21.8, 50.4, 55.6, 89.8, 115.4, 128.6, 129.0, 130.0, 130.2, 130.3, 139.9, 159.6, 159.9, 161.2

*One carbon merged with the other; [#]Viscous liquid

6.3 Hz. Four doublets each accounting for two hydrogens with a coupling constant of 8.4 Hz appear at δ 7.02, 7.34, 7.45 and 7.55. The H,H-COSY spectrum and the coupling pattern clearly reveal the presence of $\text{CH}_3\text{-CH-CH}$ grouping. The C,H-COSY spectrum reveals the chemical shift positions of the associated carbons to be δ 19.1, 90.6 and 50.3 respectively. The doublets at δ 7.02 and 7.34 belong to one aryl ring as confirmed by H,H-COSY spectrum. The signals of respective carbons appear at δ 129.5 and 129.7. The other pair of doublets at δ 7.45

and 7.55 have common H,H-COSY contour and the respective carbons appear at δ 131.2 and 129.3 respectively. The HMBC spectrum is helpful to assign the quaternary carbons of the aryl rings. Both the signals at δ 4.97 and 4.92 give HMBC contour with the carbon at δ 158.9. Obviously, this carbon must be the quaternary carbon attached to selenium. The left out carbon at δ 159.2 is attached to nitrogen. The signal at δ 4.75 gives a HMBC contour with signal at δ 159.2 and therefore that phenyl ring is at the fourth position of the selenadiazole ring.

The mass spectrum of **4e** does not exhibit the molecular ion peak. The first prominent peak that has been noticed in the higher *m/e* region is that at 286.2. This is arising due to the species, $\text{ArC} \equiv \text{CC}(\text{Ar}) = \text{CHMe}$. As there are two chlorine atoms in this species the isotope peaks at 288.5 and 290.6 also appear with an intensity ratio 9:6:1. This fragment would have obtained by the initial loss of selenium and nitrogen molecule, which is very common for the selenadiazoles of this type followed by the elimination of HNO_2 giving the conjugated fragment. The base peak appears at *m/e* 215.2. It is apparent that this species would have obtained by the cleavage of two aryl rings, the aryl at the 4th position of the selenadiazole ring and the aryl present in the side chain at C-5. This is very much unexpected as normally the selenadiazole ring gets fragmented in preference to other part of the molecule.

Thionyl chloride treatment of the semicarbazones **3** under different conditions in the expectation of preparing the respective 1,2,3-thiadiazoles **5** (**Scheme I**) did not yield the expected heterocycle, rather got hydrolyzed to give back the original ketones **2**.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Bruker 300 MHz instrument in $\text{DMSO}-d_6/\text{CDCl}_3$ using TMS as internal standard. Chemical shifts are given in δ (ppm) and coupling constants are given in Hertz. GC/MS spectra were recorded on a Thermo Finnigan gas chromatograph (RT-5 capillary column) with a Finnigan mass spectrometer operating on the electron impact mode (70 eV). Column chromatography was carried out over silica gel (60-120 mesh) using petroleum ether-ethyl acetate as an eluent.

General procedure for the preparation of 4-nitro-1,3-diaryl-1-pentanone, **2**

The adducts, 4-nitro-1,3-diaryl-1-pentanones **2** have been prepared by reported procedure⁸. A solution of nitroethane and substituted chalcones **1** was stirred in the presence of catalytic amount of sodium methoxide for about one hour at 50°C. The reaction-mixture was cooled, acidified with dilute acetic acid and then extracted with chloroform. The product obtained was crystallized from ethanol and dried. The yields are normally good in the range of 75-80%.

General procedure for the preparation of 2-[4-nitro-1,3-diarylpentylidene]-1-hydrazinecarboxamide, **3**

To a solution of 0.01 mole of the appropriate ketone **2** in 60 mL of dioxane, semicarbazide hydrochloride (0.05 mole) and sodium acetate (0.05 mole) in water (20 mL, 3:2 v/v) was added followed by a catalytic amount of phase transfer catalyst (tetrabutylammonium bromide). The reaction-mixture was stirred at RT for three days, poured onto crushed ice and extracted with chloroform. The solution was evaporated and the residue was recrystallized from ethanol to yield the major diastereomer of the semicarbazone **3**.

General procedure for the synthesis of 5-(2-nitro-1-arylpropyl)-4-aryl-1,2,3-selenadiazole, **4**

A solution of 0.005 mole of the appropriate semicarbazone **3** and 0.05 mole of powdered selenium dioxide in dry THF was gently heated on a water-bath for two hr. The selenium deposited on cooling was removed by filtration, and the filtrate was poured into crushed ice, extracted with chloroform, and purified by column chromatography using silica gel (60-120 mesh) with 97:3 petroleum ether:ethyl acetate as eluent to give the selenadiazole **4**. The solid compounds were recrystallized from ethyl alcohol.

Acknowledgement

The authors thank DST, New Delhi for IRPHA grant for NMR facility. Financial support from CSIR, New Delhi for S Saravanan is gratefully acknowledged.

References

- 1 Venulet J & VanEtten R L, *The Chemistry of Nitro and Nitroso Compounds, Part 2*, edited by H Feuer, (John Wiley and Sons. Inc, New York), **1970**, pp 201.
- 2 Zee-Cheng K & Cheng C, *J Med Chem*, **12**, **1969**, 157.
- 3 Brown A W A, Robinson D B W, Hurtig H & Wenner B J, *Can J Res*, **26D**, **1948**, 177.
- 4 Brain P W, Grove J F & McGowan J C, *Nature*, **158**, **1946**, 876.
- 5 Schales O & Graefe H A, *J Am Chem Soc*, **74**, **1952**, 4486.
- 6 Harker, *U S Patent*, **2,889,246** (**1959**); *Chem Abstr*, **53**, **1959**, 174141.
- 7 a) Saravanan S, Muthusubramanian S & Polborn K, *Indian J Chem*, **45B**, **2006**, 758; b) Saravanan S & Muthusubramanian S, *Phosphorous, Sulfur and Silicon*, **179**, **2004**, 241; c) Saravanan S, Nithya A & Muthusubramanian S, *J Heterocyclic Chem*, **43**, **2006**, 149; d) Saravanan S, Athimoolam S & Muthusubramanian S, *Arkivoc*, **2007**, 22; e) Saravanan S, Muthusubramanian S, Vasantha S, Sivakolunthu S & Raghavaiah P, *J Sulfur Chem*, **28**, **2007**, 181; f) Saravanan S, Namitharan K & Muthusubramanian S, *Indian J Chem*, **47B**, **2008**, 305.
- 8 Davey W & Tivey D J, *J Chem Soc*, **1958**, 2276.