

SYNTHESIS OF 5,7-DIPHENYL(-4-ALKYL)TRIIHYDRO PYRANO [3,4-D][1,2,3]SELENADIAZOLES AND 5,7-DIPHENYL(-4-ALKYL)TRIIHYDRO PYRANO [3,4-D][1,2,3]THIADIAZOLES

D. Bhaskar Reddy*, A. Somasekhar Reddy, V. Padmavathi and N. Chandrasekhar Babu

Department of Chemistry, S.V. University, Tirupati - 517 502, India

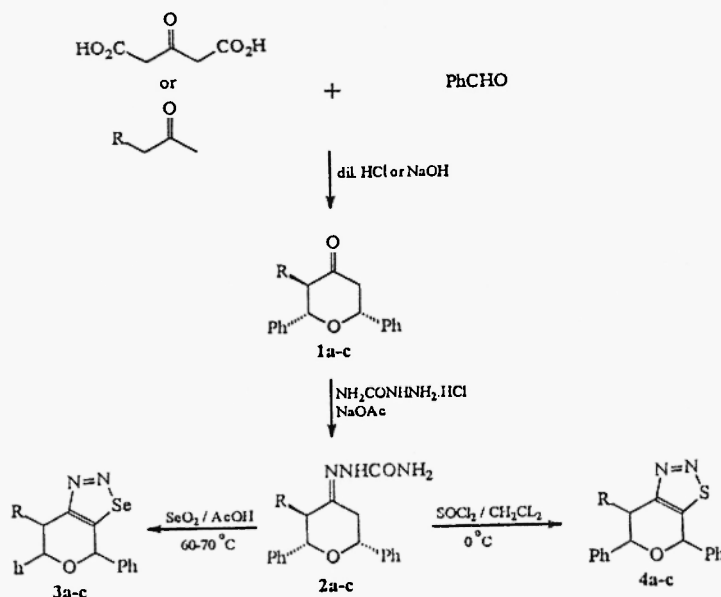
Abstract: The title compounds were prepared by the oxidative cyclization of semicarbazonetetrahydropyran with selenium dioxide and thionyl chloride.

Introduction

Among five membered heterocycles, 1,2,3-selenadiazoles and 1,2,3-thiadiazoles have received much attention due to their synthetic viability as useful compounds.¹⁻⁴ In the last couple of years our group has been actively engaged particularly in the development of 1,2,3-selena / thiadiazoles fused to a six membered cyclic system which may be a carbocycle or a heterocycle.⁵⁻⁸ In continuation of this ongoing programme, we thought of extending our studies in the development of 1,2,3-selena / thiadiazoles which were fused to a di or tri substituted tetrahydropyran. It is obvious that several natural products including antibiotics possess tetrahydropyran skeleton. In fact, this moiety is a constituent in certain basic antimicrobial agents.⁹⁻¹⁰

Results & Discussion

The successful exploitation of α -keto methylene functionality of tetrahydropyranone paved the way for the development of trihydro pyrano[3,4-d][1,2,3]selenadiazoles and thiadiazoles. The synthetic scheme involves treatment of acetone dicarboxylic acid or 2-butanone or 2-pentanone with benzaldehyde in presence of dry HCl or NaOH to prepare 2,6-diphenyl(-3-alkyl)tetrahydropyranone (**1a-c**).^{11,12} The semicarbazones of **1** (**2a-c**) on reaction with selenium dioxide at 60-70 °C led to the formation of 5,7-diphenyl(-4-alkyl)trihydropyrano[3,4-d][1,2,3] selenadiazoles (**3a-c**). On the other hand the treatment of **2** with excess thionyl chloride at 0-10 °C furnished the corresponding 5,7-diphenyl(-4-alkyl) trihydropyrano [3,4-d][1,2,3]thiadiazoles (**4a-c**) (See Scheme and Table I).



SCHEME

Table 1 : Physical Data of Compounds 3 & 4

Compd.	Yield (%)	M.P. (°C)	Mol. Formula (Mol. wt.)	Found (Calcd) %		
				C	H	N
3a	62	77-78	C ₁₇ H ₁₄ N ₂ OSe (341.27)	59.98 (59.83)	4.27 (4.13)	8.38 (8.21)
3b	65	99-101	C ₁₈ H ₁₆ N ₂ OSe (355.30)	60.97 (60.85)	4.43 (4.54)	7.75 (7.88)
3c	63	89-90	C ₁₉ H ₁₈ N ₂ OSe (369.33)	61.90 (61.79)	4.82 (4.91)	7.69 (7.58)
4a	68	102-103	C ₁₇ H ₁₄ N ₂ OS (294.39)	69.50 (69.36)	4.85 (4.79)	9.40 (9.52)
4b	65	117-118	C ₁₈ H ₁₆ N ₂ OS (308.40)	70.23 (70.10)	5.18 (5.23)	9.19 (9.08)
4c	64	109-110	C ₁₉ H ₁₈ N ₂ OS (322.43)	70.63 (70.78)	5.69 (5.62)	8.56 (8.69)

The IR spectra of **II** displayed primary bands around 3342-3430 (NHCO), 3245-3260 (CONH₂), 1696-1709 (CONH₂) and 1622-1626 (C=N). On the other hand **3** and **4** exhibited the absorption bands in the regions 1437-1462 (N=N), 685-702 (C-Se) and 668-696 (C-S) which indicates their formation. In the ¹H NMR spectra of **3a** and **4a** the methine proton at C-7 flanked between oxygen and a double bond displayed a sharp singlet at much downfield region, 3.98 and 3.99 ppm respectively. However, the protons at C-5 and C-4 ABX splitting pattern in both the compounds. The methine proton H_A coupled with methylene protons H_B and H_X and exhibited a doublet of doublet at higher L_H value. The H_B which involved in the deshielding effect of adjacent double bond undergoes similar type of couplings and appeared as a doublet of doublet at a little down field region compared to H_X (Figure). Thus, three doublet of doublets were observed in the ¹H NMR spectra of **3a** and **4a** (Table 2).

Table 2 : Spectroscopic data of Compounds 3 & 4

Compd.	IR (KBr) cm ⁻¹	¹ H NMR (CDCl ₃) δ, ppm	M ⁺
3a	1444,702	3.98 (s, 1H, C ₇ -H), 3.40 (dd, 1H, <i>J</i> = 13.6 & 4.7 Hz, C ₅ -H _X), 2.91 (dd, 1H, <i>J</i> = 13.6 & 14.5 Hz, C ₄ -H _B), 2.60 (dd, 1H, <i>J</i> = 14.5 & 4.7 Hz, C ₄ -H _A).	341, 313 234, 107, 103
3b	1462,685	3.74 (s, 1H, C ₇ -H), 3.36 (d, 1H, <i>J</i> = 10.6 Hz, C ₅ -H), 3.00 - 2.82 (m, 1H, C ₄ -H), 2.56 (d, 3H, H-CH ₃).	
3c	1437,694	3.88 (s, 1H, C ₇ -H), 3.40 (dd, 1H, <i>J</i> = 11.2 Hz, C ₅ -H), 2.98-2.86 (m, 1H, C ₄ -H), 1.94 (m, 2H, H-CH ₂ CH ₃), 0.99 (t, 3H, H-CH ₂ CH ₃).	
4a	1438,696	3.99 (s, 1H, C ₇ -H), 3.38 (dd, 1H, <i>J</i> = 14.0 & 4.7 Hz, C ₅ -H _X), 2.85 (dd, 1H, <i>J</i> = 14.0 & 12.6 Hz, C ₄ -H _B), 2.62 (dd, 1H, <i>J</i> = 12.6 & 4.7 Hz, C ₄ -H _A).	294, 266, 234, 107, 103
4b	1456,668	3.79 (s, 1H, C ₇ -H), 3.40 (d, 1H, <i>J</i> = 11.5 Hz, C ₅ -H), 2.86-2.68 (m, 1H, C ₄ -H), 1.84 (d, 3H, H-CH ₃).	
4c	1446,695	3.84 (s, 1H, C ₇ -H), 3.42 (dd, 1H, <i>J</i> = 11.0 Hz, C ₅ -H), 2.85-2.66 (m, 1H, C ₄ -H), 2.01 (m, 2H, H-CH ₂ CH ₃), 0.86 (t, 3H, H-CH ₂ CH ₃).	

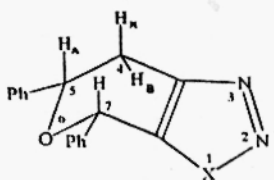


Fig.

The mass spectra (70 eV) of **3a** and **4a** showed moderately intense molecular ion peaks at m/z 341 and 294. It is of interest to note that $M+1$ ions are observed in both the systems. Expulsion of nitrogen followed by selenium / sulfur was observed in both **3a** and **4a** leading to an ion at m/z 250. The ion at m/z 103 due to styryl cation is the base peak of the spectrum in both the cases.

The compounds **3** and **4** showed the preliminary semiquantitative antimicrobial activity tests by the Vincent and Vincent method¹⁴ against the strains of bacteria (*Styphalococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Klebsiella pneumoniae*) and fungi (*Curvularia lunata*, *Fusarium solani*, *Aspergillus niger*, *Cunninghamella elegans*). Further studies of biological activity are in progress.

Experimental

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by chromatography over silica gel thin layers (Silica gel-G, hexane : ethyl acetate 3:1). IR spectra were recorded as KBr discs, using a Perkin-Elmer 993 Infrared Spectrophotometer (ν_{\max} in cm^{-1}) and ^1H NMR spectra were recorded in CDCl_3 using 200 MHz Bruker Spectrospin instrument with TMS as an internal standard (chemical shifts in ppm). The mass spectra were recorded on jeol JMS-D 300 mass spectrometer at 70 eV with as emission current of 100 μA . The elemental analyses were obtained from Micro analytical Laboratory, University of Pune, Pune, India. 2,6-Diphenyltetrahydropyran-4-one (**1a**), 3-methyl-2,6-diphenyl tetrahydropyran-4-one (**1b**), 3-ethyl-2,6-diphenyltetrahydropyran-4-one (**1c**) were prepared according to the literature procedures.^{12,13}

Preparation of 4-semicarbazono-2,6-diphenyl(-3-alkyl)tetrahydropyran (**2a-c**).

A mixture of **1** (0.01 mol), Semicarbazide hydrochloride (0.02 mol), sodium acetate (2g) in methanol (30 ml) was taken and refluxed for 4 hrs. The contents were cooled and poured onto crushed ice. The precipitated semicarbazone was filtered and dried. It was recrystallized from ethanol. **2a**, 82%, m.p. 153-54°C, **2b**, 78%, m.p. 148-49°C, **2c**, 77%, m.p. 161-62°C.

Preparation of (-3-alkyl)-4,5,7-trihydropyrano[3,4-*d*][1,2,3]selenadiazole (**3a-c**).

The semicarbazone **2** (0.005 mol) in glacial acetic acid (25 ml) was heated (60-70 °C) while stirring until the solid gets dissolved completely. To this, selenium dioxide powder (0.01 mol) was added portion wise and heating was continued until the evolution of gas ceases. Then, the reaction mixture was cooled to room temperature and filtered to remove the deposited selenium. The filtrate when poured onto crushed ice a gummy precipitate was obtained which on filtration through a column of silica gel (60-120 mesh) using ethyl acetate : pet.ether (60-80 °C) as solvent mixture gave **3**. The physical and spectroscopic data of products was listed in Tables 1&2.

Preparation of (-3-alkyl)-4,5,7-trihydropyrano[3,4-*d*][1,2,3]thiadiazole (**4a-c**).

The appropriate semicarbazone (0.005 mol) was added in portion wise into a solution of thionyl chloride (4 ml) cooled at -10 °C for a period of 30 min. After complete addition, the contents were allowed to attain room

temperature. To this dichloromethane (25 ml) was added and the excess of thionyl chloride was decomposed with saturated sodium carbonate solution. The organic layer was separated, washed with water, dried (an. Na₂SO₄) and on removal of the solvent under reduced pressure afforded the crude product which was purified by column chromatography using ethylacetate : pet. ether (60-80 °C) as eluents. The physical and spectroscopic data of products were given in Tables 1&2.

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