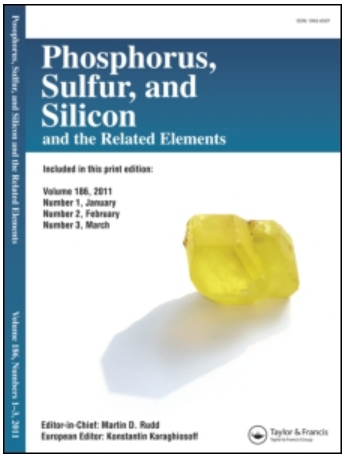

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SYNTHESIS OF SPIRO-TETRAHYDROBENZOTHIENO-1,2,3-SELENN THIADIAZOLES AND SPIRO-TETRA HYDROTHIO-CHROMENO-l,2,3-SELENA/THIADIAZOLES

D. Bhaskar Reddy[a]; M. V. Ramana Reddy[a]; A. Padmaja[a]; V. Padmavathi[a]
[a] Department of Chemistry, S.V. University, Tirupati, India

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SYNTHESIS OF SPIRO-TETRAHYDROBENZOTHIENO-1,2,3-SELENA/ THIADIAZOLES AND SPIRO-TETRA HYDROTHIO-CHROMENO-1,2,3–SELENA/THIADIAZOLES

D. BHASKAR REDDY*, M. V. RAMANA REDDY, A. PADMAJA and V. PADMAVATHI

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

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The title compounds have been prepared by exploiting α-ketomethylene group in spiro-tetrahydrobenzothienones/thiochromenones by oxidative cyclization with SeO_2 and Hurd-Mori reaction process with $SOCl_2$. The latter compounds have been obtained by the reaction of mercaptoacetic/propanoic acids with spiro-pyrimidinetriones and isoxazolidinediones followed by cyclodehydration with P_2O_5.

Keywords: tetrahydrobenzothienones; tetrahydrothiochromenones; 1,2,3-selenadiazoles; 1,2,3-thiadiazoles; cyclodehydration; condensation; Hurd-Mori reaction; oxidative cyclization

INTRODUCTION

Much emphasis has been placed on the synthesis of heterocyclic compounds resembling a steroid moiety because of the interest in their chemical and physical properties[1–3]. One such class of compounds are polycyclicpolythia compounds, which are thia-analogues of steroids. The latter, resembling gonasteroids contain heteroatoms such as N, O and S in the steroidal skeleton, but there are less reports with the other heteroatoms such as Se.

* Correspondence Author.

RESULTS AND DISCUSSION

Earlier, the *gem*-ester functionality of 2,6-dimethyl-4-oxocyclohexan-1,1 -dicarboxylates was found to be a useful one for the development of spiro-pyrimidinetriones, pyrazolidinediones and isoxazolidinediones[4,5]. Furthermore, the α-ketomethylene group in the above, has been explored to synthesize fused heterocycles[6,7]. In pursuit of this and our continued interest in the study of molecules which incorporates the 1,2,3-selena/thiadiazole group in a rigid frame work the synthesis of title compounds was carried out. The preliminary bioassay of spiro-pyrimidinetriones, pyrazolidinediones and isoxazolidinediones were found to possess antimicrobial activity[8] and as such the incorporation of 1,2,3-selena/thiadiazole moiety is expected to enhance the bioactive nature.

The condensation of **I** and **II** with thioglycolic and mercapto propanoic acid in the presence of p-toluenesulfonic acid resulted in the corresponding thioacids **III-VI** which on cyclodehydration with P_2O_5 led to the formation of **VII-X**. The semicarbazones of the latter **(XI-XIV)** by oxidative cyclization with SeO_2 and Hurd-Mori reaction process with $SOCl_2$ furnished 6,8-diarylspiro[5,6,7,8-tetrahydrobenzo[4,5]thieno[3,2-*d*][1,2,3] selena/thiadiazole-7,5′-(hexahydropyrimidine)]-2′, 4′,6′-triones(**XV/XIX**)/-7,4′-(tetrahydroisoxazole)]-3′,5′-diones **(XVI/XX)** and 7′,9′-diarylspiro [hexahydropyrimidine-5,8′-(6′,7′,8′,9′-tetrahydro-4′*H*-thiochromene[4,3-*d*] [1,2,3]selena/thiadiazole]-2,4,6-triones **(XVII/XXI)**/[tetrahydroisoxazole-4,8′-(6′,7′,8′,9′-tetrahydro-4′*H*-thiochromene[4,3-*d*][1,2,3]selena/thiadiazole)]-3,5-diones **(XVIII/XXII)** (see Scheme and Tables I & II).

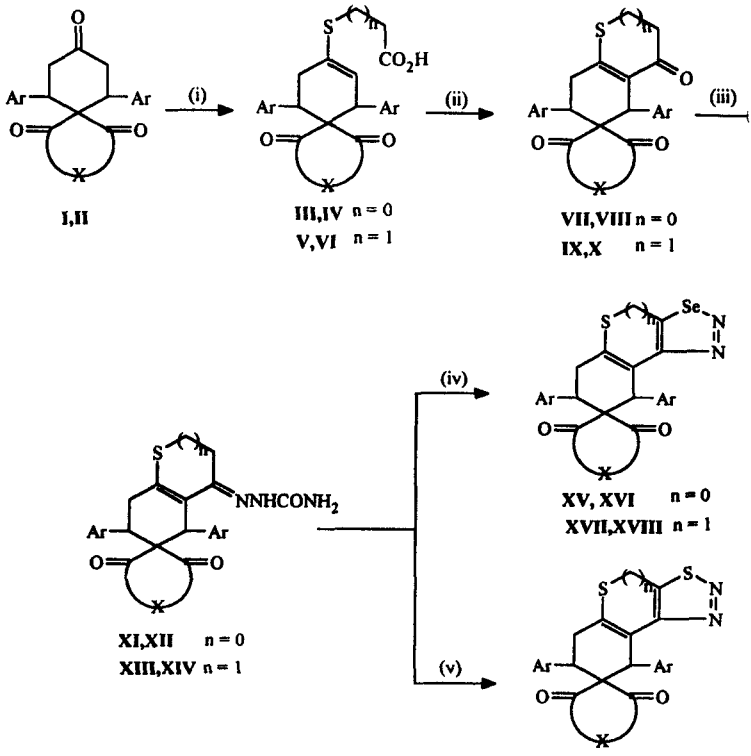
TABLE I Physical data compounds III-XIV

Compd No.	*m.p. (°C)*	*Yield (%)*	*Compd No.*	*m.p. (°C)*	*Yield (%)*
IIIa	>300	58	**IVa**	187–188	60
IIIb	274–276	62	**IVb**	244–246	61
Va	>300	55	**VIa**	202–204	55
Vb	258–260	52	**VIb**	257–259	59
VIIa	284–286	58	**VIIIa**	155–156	55
VIIb	255–256	55	**VIIIb**	223–225	59
IXa	292 (d)	62	**Xa**	177–178.5	64
IXb	224–225.5	59	**Xb**	248–250	60
XIa	>300	68	**XIIa**	224–226	70

Compd No.	m.p. (°C)	Yield (%)	Compd No.	m.p. (°C)	Yield (%)
XIb	294(d)	71	**XIIb**	254–256	65
XIIIa	>300	72	**XIVa**	202–203.5	69
XIIIb	275–277	66	**XIVb**	274(d)	72

TABLE II Melting points and analytical data of XV-XXII

Compd No.	m.p. (°C)	Yield (%)	Mol. formula (Mol.wt.)	Found (Calcd) (%)		
				C	H	N
XVa	202–204	62	$C_{23}H_{16}N_4O_3SSe$ (507.43)	54.26 (54.44)	3.26 (3.17)	11.22 (11.04)
XVb	147–149	67	$C_{25}H_{20}N_4O_5SSe$ (567.48)	53.09 (52.91)	3.42 (3.55)	9.71 (9.87)
XVIa	193–195	64	$C_{22}H_{15}N_3O_3SSe$ (480.40)	55.24 (55.00)	3.24 (3.14)	8.59 (8.74)
XVIb	133–135	59	$C_{24}H_{19}N_3O_5SSe$ (540.46)	53.59 (53.33)	3.66 (3.54)	7.94 (7.77)
XVIIa	164–166	60	$C_{24}H_{18}N_4O_3SSe$ (521.46)	55.49 (55.27)	3.30 (3.47)	10.92 (10.74)
XVIIb	174–176	63	$C_{26}H_{22}N_4O_5SSe$ (581.51)	53.84 (53.70)	3.97 (3.81)	9.79 (9.63)
XVIIIa	188–190	57	$C_{23}H_{17}N_3O_3SSe$ (494.43)	56.13 (55.87)	3.61 (3.46)	8.37 (8.49)
XVIIIb	163–165	62	$C_{25}H_{21}N_3O_5SSe$ (554.48)	54.00 (54.15)	3.94 (3.81)	7.71 (7.57)
XIXa	254–256	62	$C_{23}H_{16}N_4O_3S_2$ (460.53)	59.76 (59.98)	3.65 (3.50)	12.32 (12.16)
XIXb	169–170	63	$C_{25}H_{20}N_4O_5S_2$ (520.58)	57.84 (57.68)	3.77 (3.87)	10.60 (10.76)
XXa	>300	55	$C_{22}H_{15}N_3O_3S_2$ (433.51)	61.18 (60.95)	3.62 (3.48)	9.85 (9.69)
XXb	177–178	57	$C_{24}H_{19}N_3O_5S_2$ (493.56)	58.63 (58.40)	4.02 (3.88)	8.36 (8.51)
XXIa	202–203.5	59	$C_{24}H_{18}N_4O_3S_2$ (474.56)	60.94 (60.74)	3.93 (3.82)	11.61 (11.80)
XXIb	212–214	55	$C_{26}H_{22}N_4O_5S_2$ (534.61)	58.57 (58.41)	4.24 (4.14)	10.35 (10.47)
XXIIa	275(d)	58	$C_{23}H_{17}N_3O_3S_2$ (447.53)	61.96 (61.72)	3.69 (3.82)	9.23 (9.38)
XXIIb	237–239	59	$C_{25}H_{21}N_3O_5S_2$ (507.59)	58.95 (59.15)	4.04 (4.17)	8.46 (8.27)



SCHEME

The IR spectra of (ν, cm^{-1}) **III-VI** displayed bands around 3100–3130 (*COOH*) and 1720–1740 (*COOH*) indicating their formation. The presence of absorption bands around 1610–1710 (C=O) and the absence of bands corresponding to carboxylic group supports that cyclization indeed has taken place leading to **VII-X**. The characteristic absorption bands for

semicarbazone moiety around 3230–3260 (NH_2), 3410–3440 (NH), 1705–1725 (C=O) and 1425–1440 (C=N) were exhibited by **XI-XIV**. The absorption bands observed in the regions 1505–1555 (N=N), 695–710 (C-Se), 670–690 cm^{-1} (C-S) evidenced the formation of **XV-XXII**.

The ^1H NMR spectra (δ, ppm) of **XV, XVI, XIX** and **XX** showed sharp singlets at downfield region around 5.30–5.50 for the methine protons (C_8-H) due to anisotropic effect of adjacent double bond. However, **XVII, XVIII, XXI** and **XXII** exhibited two sharp singlets for methylene (C_4'-H) and methine protons (C_9'-H) around 3.02–3.10 and 5.40–5.45 respectively. On the other hand, the methylene and methine protons [C_5-H, H_B&H_X; C_6-H, H_A] in **XV, XVI, XIX**and **XX** and [C_6'-H, H_B&H_X; C_7'-H, H_A] in **XVII, XVIII, XXI** and **XXII** of the basic moiety exhibited ABX splitting pattern. The H_A, H_B and H_X appeared as doublet of doublets due to vicinal and geminal couplings and appeared around 4.18–4.34, 3.50–3.59 and 2.80–2.86 and 4.24–4.37, 3.42–3.55 and 2.68–2.87 respectively (see Tables III & IV).

TABLE III PMR spectral data of compounds XV, XVI, XIX and XX

Compd No.	*^1H NMR ($CDCl_3$) δ, ppm*					*Coupling constants, Hz*		
	C_8-H	C_6-H_A	C_5-H_B	C_5-H_X	NH	J_{AB}	J_{BX}	J_{AX}
XVa	5.48	4.26	3.50	2.82	11.02	12.5	14.8	4.6
XVIb	5.32	4.18	3.53	2.86	11.05	12.5	15.0	4.7
XIXb	5.51	4.34	3.56	2.84	10.62	13.8	14.9	4.5
XXa	5.36	4.28	3.59	2.85	10.84	12.7	14.7	4.5

TABLE IV PMR spectral data of compounds XVII, XVIII, XXI and XXII

Compd No.	*^1H NMR ($CDCl_3$) δ, ppm*						*Coupling constants, Hz*		
	C_4'-H	C_9'-H	C_7'-H_A	C_6'-H_B	C_6'-H_X	NH	J_{AB}	J_{BX}	J_{AX}
XVIIb	3.02	5.46	4.34	3.42	2.82	11.04	13.8	14.5	4.5
XVIIIa	3.04	5.39	4.24	3.43	2.68	10.09	13.5	14.2	4.6
XXIa	3.08	5.48	4.37	3.55	2.87	10.65	13.6	14.8	4.5
XXIIb	3.02	5.29	4.24	3.54	2.85	10.72	12.7	14.8	4.6

Antimicrobial activity

The lead compounds showed in the first preliminary semiquantitative antimicrobial tests by the paper disc method[9,10], a promising activity against several strains of bacteria, *Staphylococcus aureus, Bacillus subtilis* (gram +ve) and *Escherichia coli* (gram -ve) and fungi, *Curvularia lunata, Fusarium solani* and *Helminthosporium oryzae*. Further detailed studies of biological activity of these compounds are in progress.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel-G, BDH, hexane:ethyl acetate, 3:1). The IR spectra were recorded on a Perkin-Elmer Grating Infrared Spectrophotometer Model 337 in KBr pellets. The ^{1}H NMR spectra were scanned in $CDCl_3$/DMSO-d_6 on a Bruker Spectrospin Varian EM-360 Spectrophotometer with TMS as an internal standard. The elemental analyses were performed by Dr.Reddy's Research Foundation, Hyderabad, A.P., India.

General procedure for the preparation of 2-(1,3,5-trioxo-7,11-diaryl-2,4-diazaspiro[5,5]undec-8-en-ylsulfanyl) acetic acid (III) / 3-(1,3,5-trioxo-7,11-diaryl-2,4-diazaspiro[5,5]undec-8-en-ylsulfanyl) propanoic acid (V) and 2-(1,4-dioxo-6,10-diaryl-2-oxa-3-azaspiro[4,5]dec-7-en-8-ylsulfanyl) acetic acid (IV) / 3-(1,4-dioxo-6,10-diaryl-2-oxa-3-azaspiro[4,5]dec-7-en-8-ylsulfanyl) propanoic acid (VI)[1,2]

An equimolar mixture of spiro-pyrimidinetrione **(I)**/isoxazolidinedione **(II)** (10 mmol), mercaptoacetic acid / 3-mercaptopropanoic acid thiophene free dry benzene (60–70 ml) was taken in a round bottomed flask provided with a Dean-starks apparatus. To this, a catalytic amount of p-toluenesulfonic acid (500 mg) was added and refluxed over an oil bath (110–120°C) for a period of 20–24 h. Then the contents were cooled and washed thoroughly with water and extracted with saturated sodium bicarbonate solution.

The aqueous extracts were acidified with ice-cold concentrated hydrochloric acid. The product separated was extracted with chloroform and

then dried. Evaporation of the solvent gave a gummy substance. It was filtered through a column of silica gel to get **III-VI**.

General procedure for the preparation of 4,6-diarylspiro[2,3,4,5,6,7-hexahydrobenzo[*b*]thiophene-5,5′-(hexahydropyrimidine)] -2′,3,4′,6′-tetrones (VII); 5′,7′-diarylspiro[hexahydropyrimidine-5,6′-(3′,4′,5′,6′,7′,8′-hexahydro-2′*H*-thiochromene)]-2,4,4′,6-tetrones (IX) and 4,6-diarylspiro[2,3,4,5,6,7-hexahydrobenzo[*b*]thiophene-5,4′-(tetrahydroisoxazole)]-3,3′,5′-triones (VIII) and 5′,7′-diarylspiro [tetrahydroisoxazole-4,6′-(3′,4′,5′,6′,7′,8′-hexahydro-2′H-thiochromene)]-3,4′,5-triones (X)[1,2]

The acid **(III-VI)** (10 mmol) in dry benzene (30 ml) and an excess of phosphorus pentoxide (10 g) were taken and refluxed for 10–12 h using Dean-Starks apparatus. After completion of the reaction, the contents were cooled and extracted with benzene. The combined benzene extracts were washed with water, saturated sodium bicarbonate solution and again with water and dried. The solvent was evaporated to get a syrupy substance, which was subjected to column chromatography to afford pure **VII-X**.

General procedure for the preparation of 3-semicarbazono 4,6-diarylspiro-[2,3,4,5,6,7-hexahydrobenzo[b]thiophene-5,5′-(hexahydropyrimidine)]-2′,4′,6′-triones (XI); 4′-semicarbazono 5′,7′-diarylspirohexahydropyrimidine-5,6′-(3′,4′,5′,6′,7′,8′-hexahydro-2′*H*-thiochromene)]-2,4,6-triones (XIII); 3-semicarbazono 4,6-diarylspiro [2,3,4,5,6,7-hexahydrobenzo[*b*]thiophene-5,4′-(tetrahydroisoxazole)]-3′,5′-diones (XII) and 4′-semicarbazono 5′,7′-diarylspiro[tetrahydroisoxazole-4,6′-(3′,4′,5′,6′,7′,8′-hexahydro-2′*H*-thiochromene)]-3,5-diones (XIV)[11]

An equimolar (10 mmol) mixture of thioketocompound **(VII-X)**, semicarbazide hydrochloride, sodium acetate and methanol (50 ml) was taken in a round bottomed flask fitted with a reflux condenser and heated on a water bath for 7–10 h. The reaction mixture was then concentrated, cooled and poured onto crushed ice. The product separated was filtered, dried and recrystallized from alcohol to get pure **XI-XIV**.

General procedure for the preparation of 6,8-diarylspirol[5,6,7,8-tetrahydrobenzo[4,5]thieno[3,2-*d*][1,2,3]selenadiazole-7,5′-(hexahydropyrimidine)]-2′,4′,6′-triones (XV); 7′,9′-diarylspiro[hexahydropyrimidine-5,8′-(6′,7′,8′,9′-tetrahydro-4′*H*-thiochromene[4,3-*d*] [1,2,3] selenadiazole)]-2,4,6-triones (XVII), 6,8-diarylspiro-[5,6,7,8-tetrahydrobenzo[4,5]thieno[3,2-*d*][1,2,3]selenadiazole-7,4′-(tetrahydro-isoxazole)]-3′,5′-diones (XVI) and 7′,9′-diarylspiro[tetrahydroisoxazole-4,8′-(6′,7′,8′,9′-tetrahydro-4′*H*-thiochromene[4,3-*d*][1,2,3]selenadiazole)]-3,5-diones (XVIII)[12]

Semicarbazone of thioketocompound (**XI-XIV**) (10 mmol) was dissolved in glacial acetic acid (5 ml) and warmed gently while stirring. To this, selenium dioxide powder (10 mmol) was added in portion wise and stirred until the evolution of gas ceased. Then the contents were cooled and allowed to attain room temperature. The selenium deposited was separated by filtration. The resultant filtrate was poured onto crushed ice and the solid separated was washed thoroughly with cold water and sodium bicarbonate. It was purified over a column of silica gel to get **XV-XVIII**.

General procedure for the preparation of 6,8-diarylspiro[5,6,7,8-tetrahydrobenzo-[4,5]thieno[3,2-*d*][1,2,3]thiadiazole-7,5′-(hexahydropyrimidine)]-2′,4′,6′-triones (XIX), 7′,9′-diarylspiro[hexahydropyrimidine-5,8′-(6′,7′,8′,9′-tetrahydro-4′*H*-thiochromene [4,3-*d*][1,2,3] thiadiazole)]-2,4,6-triones (XXI); 6,8-diarylspiro[5,6,7,8-tetrahydro-benzo[4,5]thieno[3,2-*d*][1,2,3]thiadiazole-7,4′-(tetrahydro-isoxazole)-3′,5′-diones (XX) and 7′,9′-diarylspiro[tetrahydroisoxazole-4,8′-(6′,7′,8′,9′-tetrahydro-4′*H*-thiochromene[4,3-*d*][1,2,3]thiadiazole)]-3,5-diones (XXII)[13]

To a well cooled solution of thionyl chloride (5 ml), semicarbazones of thioketocompound (**XI-XIV**)(10 mmol) was added in small quantities while maintaining the temperature −10°C. It was then allowed to attain room temperature and after that dichloromethane (10–15 ml) and saturated sodium carbonate solution was added. The organic layer was separated and washed repeatedly with water and dried. The solvent was evaporated off. The gummy product so obtained was purified through a column of silica gel to furnish **XIX-XXII**.

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