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Note

Synthesis of 1,3,5-triazinane-2-thiones and 1,3,5-oxadiazinane-4-thiones linked with isoxazoles

E Rajanarendar*, A Siva Rami Reddy & Firoz Pasha Shaik

Department of Chemistry, Kakatiya University, Warangal 506 009, India

E-mail: eligeti_rajan@yahoo.co.in

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Trimolecular condensation of *N*-(3,5-dimethyl-4-isoxazolyl)-*N*'-arylthioureas **2** obtained from **1** by reaction with arylisothiocyanates, with aqueous formaldehyde and primary amines in toluene under reflux leads to 5-alkyl-1-(3,5-dimethyl-4-isoxazolyl)-3-aryl-hexahydro-1,3,5-triazinane-2-thiones **3** in excellent yields. Condensation of **2** with aqueous formaldehyde under similar condition provides isoxazolyl 1,3,5-oxadiazinane-4-thiones **4**.

Keywords: Isoxazolyl trizinane-2-thiones, trimolecular condensation, isoxazolyl oxadiazinane-4-thiones

Heterocycles are widely utilized compounds in both pharmaceutical and agricultural fields[1]. Consequently, the development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities. Among aromatic heterocycles, the isoxazole unit constitutes an easily accessible nucleus that is present in a number of natural and pharmacological compounds[2] and displays a wide range of organic reactivities and could be used as an effective means of preparing new molecular scaffolds[3]. Isoxazoles have been repeatedly shown as useful synthons in organic synthesis[4].

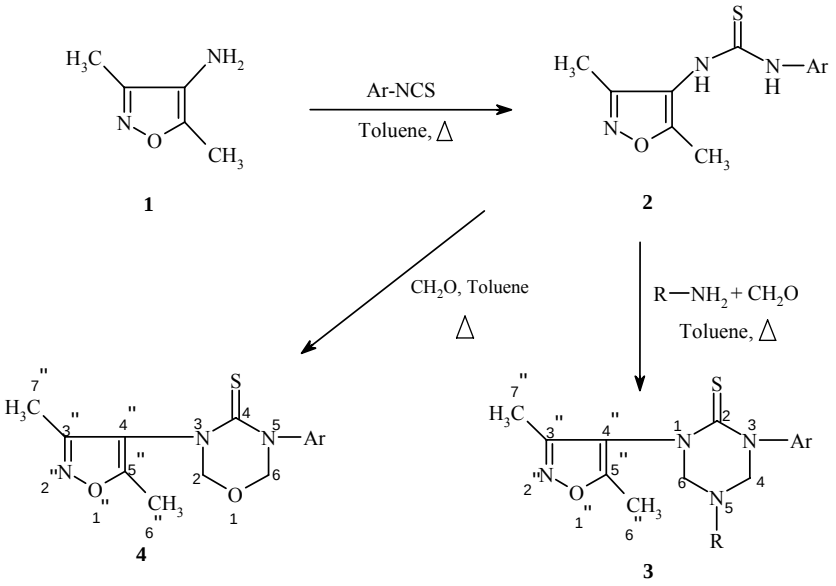
1,3,5-Triazinane-2-ones are useful for protection of amino groups[5], as well as for the synthesis of polyamines[6], polyfunctional amino alcohols[5] and water soluble triazinane-2-ones were used as fertilizers[7]. Very few reports are available on the synthesis of heterocyclic 1,3,5-triazinane-2-ones[8,9] and 1,3,5-oxadiazinane-4-ones[10] as well as on the synthesis of unsymmetrical triazinethiones and oxadiazine thiones[11]. The synthesis of triazinane-2-thiones involves a one-pot three-component procedure. Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry[12]. In these procedures, a number of building blocks come together in a single reaction vessel to form a new product in which each individual component is contained. Therefore, in MCRs, a high degree of molecular diversity can be introduced by variation of a single component at a time.

Literature survey reveals that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity[13,14] was produced. The chemistry of these linked bi-heterocycles has been a fascinating field of investigation in medicinal chemistry, as they have been found to exhibit enhanced biological profile[15]. In view of these observations and also as a sequel to our work on the synthesis of a variety of heterocycles linked with isoxazole ring[16], it was thought worthwhile to synthesize novel bi-heterocycles containing isoxazole unit, in order to explore the pharmacological activity of these compounds. In the present paper synthesis of unsymmetrical triazinane-2-thiones and oxadiazinane-4-thiones linked with isoxazole unit is reported.

Results and Discussion

3,5-Dimethyl-4-nitroisoxazole[17] on reduction with Zn dust and ammonium chloride resulted 4-amino-3,5-dimethylisoxazole **1** (Ref. 17). The reaction of 4-amino-3,5-dimethylisoxazole **1** with aryl isothiocyanates in toluene under reflux condition afforded *N*-(3,5-dimethyl-4-isoxazolyl)-N'-arylthioureas **2** (Refs. 18,19) in excellent yields. The trimolecular condensation of primary amines, *N,N'*-unsymmetrical disubstituted thioureas **2** and 30% formaldehyde in toluene led to the formation of new 5-alkyl-1-(3,5-dimethyl-4-isoxazolyl)-3-aryl-hexahydro-1,3,5-triazinane-2-thiones **3** in high yields. Similarly, condensation of *N,N*'-unsymmetrical disubstituted thioureas **2** and 30% formaldehyde in toluene under reflux condition resulted new 5-aryl-3-(3,5-dimethyl-4-isoxazolyl)-2,3,5,6-tetrahydro-4*H*-1,3,5-oxadiazinane-4-thiones **4** in good yields (**Scheme I**).

Formaldehyde reacts with the primary amine to give an iminium species, which then reacts with the nitrogen atom of *N,N*'-unsymmetrical disubstituted thioureas **2** to form the first N-C-N bond. Thermal



1 **2** **4** **3**

2, 4a = Ar = C_6H_5
2, 4b = Ar = C_6H_4-Br (p)
2, 4c = Ar = C_6H_4-CH_3 (p)
2, 4d = Ar = C_6H_4-OCH_3 (p)
2, 4e = Ar = C_6H_4-Cl (p)

3a = Ar = C_6H_5, R = CH_3
3b = Ar = C_6H_4-Br (p), R = CH_3
3c = Ar = C_6H_4-CH_3 (p), R = CH_2CH_3
3d = Ar = C_6H_4-OCH_3 (p), R = CH_2CH_3
3e = Ar = C_6H_4-Cl (p), R = CH_2CH_3

Scheme I

generation of second iminium electrophile triggers ring closure to give the triazinane-thione **3**. Formation of oxadiazinane-thione **4** could occur by the nucleophilic attack of urea nitrogen on formaldehyde followed by dehydration.

In summary, an efficient method for the syntheses of novel triazinanethiones and oxadiazinanethiones by trimolecular condensation and two-component condensation respectively on isoxazole unit is developed.

In view of potential activity of these compounds, it is predicted that the newly synthesized isoxazolyl triazinonethiones and oxadiazinonethiones may possess biological activity and the activity data will be published elsewhere.

Experimental Section

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. Visualization was done by exposing to iodine vapour. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethyl silane as internal standard. ^{13}C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyser. Column chromatography was conducted by using silica gel (60-120 mesh, Merck) with solvent system benzene:ethyl acetate (1:1) as elute.

General procedure for the synthesis of isoxazolyl-triazinane-2-thiones 3

(a) Preparation of *N*-(3,5-dimethyl-4-isoxazolyl)-*N*'-arylthioureas 2 (Ref. 18,19): To a solution of 4-amino-3,5-dimethylisoxazole **1** (0.01 mole) in toluene (20 mL), was added aryl isothiocyanate (0.01 mole), and the contents were refluxed for 6 hr. The reaction was monitored with TLC. After the completion of the reaction, it was cooled and the separated product was filtered and crystallized from benzene.

b) Preparation of 5-alkyl-1-(3,5-dimethyl-4-isoxazolyl)-3-aryl-hexahydro-1,3,5 triazinane-2-thiones 3: A mixture of *N*,*N'*-unsymmetrical disubstituted thiourea **2** (0.01 mole), 30% formaldehyde (0.01 mole) and primary amine (0.01 mole) in toluene (15 mL) were heated under reflux for 6 hr. The solvent

was distilled off under reduced pressure, the resultant gum product was triturated with pet. ether repeatedly to get the solid compound. The crude product was chromatographed over a silica gel column. Elution with benzene: ethyl acetate (1:1) afforded triazinan-thione.

Compound 3a: White crystalline solid, yield 80%, m.p. 165-67°C, IR (KBr): 1232 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.0 (s, 3H, -NCH_3), 4.5 (s, 2H, CH_2), 4.6 (s, 2H, CH_2), 7.2-7.6 (m, 5H, ArH); C^{13} NMR (75 MHz,$CDCl_3$): δ 10.48 (C-6"), 11.41(C-7"), 40.33 (N-CH_3),71.91 (C-4), 72.70 (C-6), 119.68 (C-4"), 120.65 (Ar-C),127.97 (Ar-C),129.31 (Ar-C),129.71 (Ar-C),130.04 (Ar-C),144.25 (Ar-C)158.44 (C-3"),164.69 (C-5"),180.25 (C-2). MS(EI): *m/z* 303 $[M+H]^+$. Anal. Calcd for $C_{15}H_{18}N_4OS$: C, 59.58; H, 6.00; N,18.53. Found: C, 59.55; H, 5.91; N, 18.61%.

Compound 3b: White crystalline solid, yield 80%, m.p. 195-97°C, IR (KBr): 1220 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.2 (s, 3H, -NCH_3), 4.6 (s, 2H, CH_2), 4.8 (s, 2H, CH_2), 7.2-7.4 (d, 2H, *J* = 8.0 Hz, ArH), 7.6-7.8 (d,2H,*J* = 8.0 Hz,ArH); MS(EI): *m/z* 381 $[M+H]^+$. Anal. Calcd for $C_{15}H_{17}N_4OSBr$: C, 47.25; H, 4.49; N, 14.69. Found: C, 47.18; H, 4.48; N, 14.73%.

Compound 3c: White crystalline solid, yield 75%, m.p. 175-77°C, IR (KBr): 1225 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.2 (t, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 3.2 (q, 2H, CH_2), 4.5 (s, 2H, CH_2), 4.6 (s, 2H, CH_2), 7.0-7.4 (m, 4H, ArH); MS(EI): *m/z* 331 $[M+H]^+$. Anal. Calcd for $C_{17}H_{22}N_4OS$: C, 61.79; H, 6.71; N, 16.95. Found: C, 61.83; H, 6.72; N, 16.92%.

Compound 3d: White crystalline solid, yield 80%, m.p.150-52°C, IR (KBr): 1230 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.2 (t, 3H, CH_3), 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.2 (q, 2H, CH_2), 3.8 (s, 3H, OCH_3), 4.4 (s, 2H, CH_2), 4.6 (s, 2H, CH_2), 7.1-7.5 (m, 4H, ArH); MS (EI): *m/z* 347 $[M+H]^+$. Anal. Calcd for $C_{17}H_{22}N_4O_2S$: C, 58.94; H, 6.40; N, 16.17. Found: C, 58.91; H, 6.39; N, 16.12%.

Compound 3e: White crystalline solid, yield 75%, m.p. 180-82°C, IR (KBr): 1220 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.2 (t, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.2 (q, 2H, CH_2), 4.5 (s, 2H, CH_2), 4.7 (s, 2H, CH_2), 7.0-7.3 (d, 2H, *J = 7.8 Hz,* ArH), 7.4-7.6 (d, 2H, *J* = 7.8 Hz, ArH); MS(EI): *m/z* 351 $[M+H]^+$. Anal. Calcd for $C_{16}H_{19}N_4OSCl$: C, 54.77; H, 5.46; N, 15.97. Found: C, 54.81; H, 5.49; N, 16.05%.

General procedure for the synthesis of 5-aryl-3-(3,5-dimethyl-isoxazol-4-yl)-2,3,5,6-tetrahydro-4*H*-1,3,5-oxadiazinane-4-thiones, 4

N,N'- Unsymmetrical disubstituted thiourea **2** (0.01 mole) was added with stirring to a solution of 30% formaldehyde (0.02 mole) and the mixture was treated with Conc. HCl (1 mL). After heating it at 90-95°C for 4 hr (monitored by TLC), the reaction-mixture was cooled and neutralized with NaOH. The solid thus obtained was filtered off and chromotographed using silica gel column. Elution with benzene:ethyl acetate (1:1) afforded the oxadiazinan-thiones.

Compound 4a: White crystalline solid, yield 75%, m.p. 141-43°C, IR (KBr): 1120 (C-O-C), 1230 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.9 (s, 2H, CH_2), 5.0 (s, 2H, CH_2), 7.0-7.6 (m, 5H, ArH); C^{13} NMR (75 MHz,$CDCl_3$): δ 9.91 (C-6"),11.41 (C-7"), 87.23 (C-2),88.44 (C-6), 119.68 (C-4"), 124.97 (Ar-C), 127.31(Ar-C), 129.08 (Ar-C), 129.61 (Ar-C), 131.04 (Ar-C) 144.66 (Ar-C), 158.70 (C-3"), 164.63 (C-5"), 180.81 (C-4); MS(EI): *m/z* 290 $[M+H]^+$. Anal. Calcd for $C_{14}H_{15}N_3O_2S$: C, 58.11; H, 5.23; N, 14.52. Found: C, 58.10; H, 5.24; N, 14.59%.

Compound 4b: White crystalline solid, yield 75%, m.p. 163-65°C, IR (KBr): 1120 (C-O-C), 1225 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.8 (s, 2H, CH_2), 5.0 (s, 2H, CH_2), 7.3-7.4 (d, 2H, *J* = 7.9 Hz,ArH), 7.6-7.7 (d, 2H, *J*=7.9 Hz, ArH); MS(EI): *m/z* 368 $[M+H]^+$. Anal. Calcd for $C_{14}H_{14}N_3O_2SBr$: C, 45.66; H, 3.83; N, 11.41. Found : C, 45.72; H, 3.71; N, 11.49%.

Compound 4c: White crystalline solid, yield 70%, m.p. 133-35°C, IR (KBr): 1120 (C-O-C), 1232 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 2.1 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 4.8 (s, 2H, CH_2), 5.0 (s, 2H, CH_2), 7.0-7.1 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.2-7.5 (d, 2H, *J*=7.8 Hz, ArH); MS(EI): *m/z* 304 $[M+H]^+$. Anal. Calcd for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.65; N, 13.85. Found: C, 59.33; H, 5.69; N, 13.89%.

Compound 4d: White crystalline solid, yield 70%, m.p. 137-39°C, IR (KBr): 1125 (C-O-C), 1230 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.8 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 7.2-7.6 (m, 4H, ArH); MS(EI): *m/z* 320 $[M+H]^+$. Anal. Calcd for $C_{15}H_{17}N_3O_3S$: C, 56.41;

H, 5.37; N, 13.16. Found: C, 56.47; H, 5.25; N, 13.09%.

Compound 4e: White crystalline solid, yield 75%, m.p. 155-57°C, IR (KBr): 1120 (C-O-C), 1230 (C=S) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.8 (s, 2H, CH_2), 5.0 (s, 2H, CH_2), 7.2 (d, 2H, *J = 8.0* Hz, Ar-H), 7.5 (d, 2H, *J = 8.0* Hz, ArH); MS(EI): *m/z* 324 $[M+H]^+$. Anal. Calcd for $C_{14}H_{14}N_3O_2SCl$: C, 51.93; H, 4.36; N, 12.98. Found: C, 52.00; H, 4.30; N, 13.03%.

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