A Simple Method for the Synthesis of 5-Isoxazolyl-4-thioxo-1,3,5-benzoxadiazocines

E. Rajanarendar,* E. Kalyan Rao, and A. Siva Rami Reddy

Department of Chemistry, Kakatiya University, Warangal 506 009, Andhra Pradesh, India
*E-mail: eligeti_rajan@yahoo.co.in

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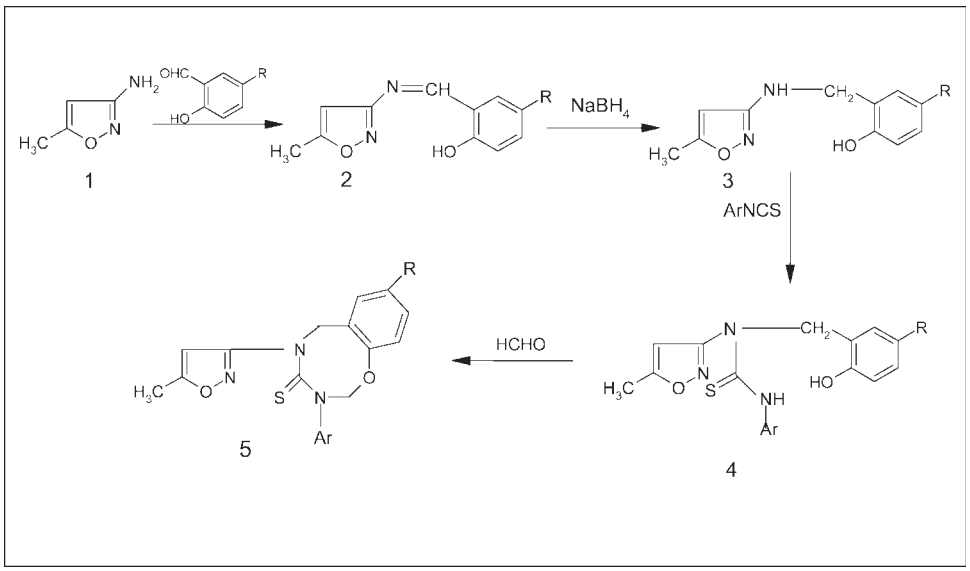

Synthesis of novel isoxazolyl 1,3,5-benzoxadiazocines **5** has been accomplished by condensation of 3-amino-5-methylisoxazole **1** with salicylaldehydes, followed by reduction, treatment with arylisothiocyanates, and subsequent ring closure in the presence of formaldehyde. The methodology used in this synthesis is the first approach of its kind.

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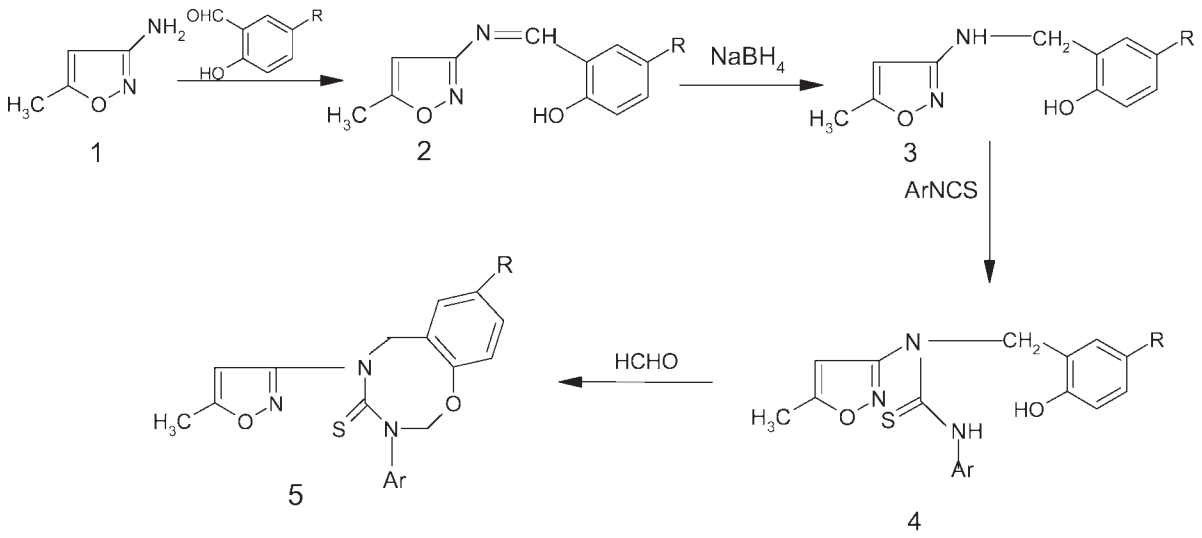
INTRODUCTION

Benzoxadiazocines have been claimed to exhibit sedative, muscle relaxant and anticonvulsant effects [1]. Oxadiazocines are shown to act as bacteriocides, hypnotic agents [2], central nervous system stimulants [3], and are also known to possess pharmacological activity [4]. The biological importance and considerable therapeutic potential of these compounds generated interest in designing the synthesis of a number of derivatives [5], which might become potential drug candidates as inhibitors of HIV-1 reverse transcriptase [6]. Very recently, oxadiazocines are reported to have been used as immuno therapeutics, antimicrobial drugs, and vaccines [7]. Similarly isoxazole nucleus can be found frequently in the structure of numerous naturally occurring and synthetic compounds with interesting biological and pharmacological properties [8]. In spite of such a high potential significance for benzoxadiazocines and oxadiazocines, a survey of literature showed that little attention has been given toward the synthesis of this class of heterocyclic compounds. In view of this, and as a sequel to our work on the synthesis of a variety of heterocycles linked to the isoxazole moiety [9], we undertook the synthesis of isoxazolyl benzoxadiazocines to explore the pharmacological activity of these compounds. Herein, we present our results on the synthesis of isoxazolyl 1,3,5-benzoxadiazocines by adopting simple methodology.

RESULTS AND DISCUSSION

The reaction of 3-amino-5-methylisoxazole **1** with substituted salicylaldehydes in hot alcohol led to the formation of Schiff bases **2** in quantitative yields. The Schiff bases **2** on reduction with sodium borohydride produced 2-[(5-methyl-isoxazol-3-yl-amino)-methyl] phenols **3** in moderate to good yields. The nucleophilic addition of amino methyl phenols **3** with aryl isothiocyanates has been carried out in hot chloroform with stirring for 6 h. The resulting product has been identified as *N*-(5-methyl-isoxazol-3-yl)-*N*-(2-hydroxybenzyl)-*N*′-aryl thioureas **4**. The thioureas **4** on heating with formaldehyde in methanol solution underwent ring closure, involving an internal Mannich reaction, to give novel

Scheme 1



2, 3a	= R = H	**4, 5a**	= R = H, Ar = C_6H_5
2, 3b	= R = CH_3	**4, 5b**	= R = H, Ar = C_6H_4-Cl(p)
2, 3c	= R = OCH_3	**4, 5c**	= R = H, Ar = C_6H_4-Br(p)
2, 3d	= R = Cl	**4, 5d**	= R = H, Ar = C_6H_4-CH_3(p)
2, 3e	= R = Br	**4, 5e**	= R = CH_3, Ar = C_6H_5
		4, 5f	= R = OCH_3, Ar = C_6H_5

5-(5-methyl-isoxazol-3-yl)-3-aryl-3,4,5,6-tetrahydro-2*H*-1,3,5-benzoxadiazocine-4-thiones **5** in moderate to good yields (Scheme 1).

It can be concluded that a simple and efficient method to synthesize isoxazolyl benzoxadiazocines in good yields under mild conditions has been achieved. It is possible that these compounds may have applications as drugs; the activity data will be published elsewhere. This happens to be the first report on the synthesis of benzoxadiazocines linked to an isoxazole unit.

EXPERIMENTAL

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 vapor IR spectra (KBr pellet) were recorded on Perkin-Elmer BX series FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethylsilane as internal standard. 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 analyzer.

General procedure for the preparation of 2-[(5-methyl-3-isoxazolyl)imino]methylphenols (2a–2e). 3-Amino-5-methyl-isoxazole **1** (0.01 mol) and salicylaldehyde (0.01 mol) were refluxed in ethanol (10 mL) for 2 h. The solution was cooled and the separated solid was collected by filtration and re-crystallized from pet ether.

2-[(5-Methyl-3-isoxazolyl)imino]methylphenol (2a). This compound was obtained as yellow crystals, yield 95%; mp 57–59°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 5.95 (s, 1H, isoxazole-H), 6.82–7.55 (m, 4H, ArH), 8.82 (s, 1H, —N=CH—), 12.02 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 203 (M + H^+); IR (KBr): 3400 (O—H), 1607 (C=N), 1577, 1400 (C=C), 1282 cm^{-1} (C—O). *Anal*. Calcd. for $C_{11}H_{10}N_2O_2$ (202): C, 65.34; H, 4.95; N, 13.86. Found: C, 65.38; H, 5.10; N, 13.79.

4-Methyl-2-[(5-methyl-3-isoxazolyl)imino]methylphenol (2b). This compound was obtained as yellow crystals, yield 90%; mp 68–70°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.02 (s, 1H, isoxazole-H), 6.80–7.50 (m, 3H, ArH), 8.75 (s, 1H, —N=CH—), 12.85 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 217 (M + H^+); IR (KBr): 3390 (O—H), 1615 (C=N), 1580, 1450 (C=C), 1275 cm^{-1} (C—O). *Anal*. Calcd. for $C_{12}H_{12}N_2O_2$ (216): C, 66.66; H, 5.55; N, 12.96. Found: C, 66.60; H, 5.62; N, 12.90.

4-Methoxy-2-[(5-methyl-3-isoxazolyl) imino] methyl phenol (2c). This compound was obtained as yellow crystals, yield 90%; mp 80–82°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 6.12 (s, 1H, isoxazole-H), 6.80–

7.10 (m, 3H, ArH), 8.80 (s, 1H, —N=CH—), 12.05 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 233 ($M + H^+$); IR (KBr): 3385 (O—H), 1620 (C=N), 1575, 1425 (C=C), 1280 cm^{-1} (C—O). *Anal*. Calcd. for $C_{12}H_{12}N_2O_3$ (232): C, 62.06; H, 5.17; N, 12.06. Found: C, 62.15; H, 5.13; N, 12.14.IR.

4-Chloro-2-[(5-methyl-3-isoxazolyl)imino]methylphenol (2d). This compound was obtained as yellow crystals, yield 88%; mp 93–95°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 5.90 (s, 1H, isoxazole-H), 7.50–8.02 (m, 3H, ArH), 8.85 (s, 1H, —N=CH—), 12.50 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 237 ($M + H^+$); IR (KBr): 3405 (O—H), 1615 (C=N), 1580, 1400 (C=C), 1275 cm^{-1} (C—O). *Anal*. Calcd. for $C_{11}H_9N_2O_2Cl$ (236): C, 55.93; H, 3.81; N, 11.86. Found: C, 56.05; H, 3.85; N, 11.88.

4-Bromo-2-[(5-methyl-3-isoxazolyl)imino]methylphenol (2e). This compound was obtained as yellow crystals, yield 95%; mp 110–112°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 6.02 (s, 1H, isoxazole-H), 7.70–8.02 (m, 3H, ArH), 8.90 (s, 1H, —N=CH—), 12.40 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 281 ($M + H^+$); IR (KBr): 3368 (O—H), 1612 (C=N), 1489 (C=C), 1275 cm^{-1} (C—O). *Anal*. Calcd. for $C_{11}H_9N_2O_2Br$ (280): C, 47.14; H, 3.21; N, 10.00. Found: C, 47.20; H, 3.29; N, 9.95.

General procedure for the preparation of 2-[(5-methyl-3-isoxazolyl)amino]methyl phenols (3a–3e). To an ethanolic solution (10 mL) of Schiff base **2** (0.01 mol) sodium borohydride (0.02 mol) was slowly added with stirring. The reaction was conducted at room temperature with stirring for 30 min. The solid that separated on pouring the reaction mixture into ice-cold water was collected filtration and re-crystallized from ethanol.

2-[(5-Methyl-3-isoxazolyl)amino]methylphenol (3a). This compound was obtained as brown crystals, yield 82%; mp 85–87°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 3H, CH_3), 4.31 (s, 2H, —CH_2—), 5.20 (bs, 1H, NH, D_2O exchangeable), 5.66 (s, 1H, isoxazole-H), 6.80–7.25 (m, 4H, ArH), 9.45 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 205 ($M + H^+$); IR (KBr): 3640 (N—H), 3376 (O—H), 1631 (C=N), 1458 (C=C), 1210 cm^{-1} (C—O). *Anal*. Calcd. for $C_{11}H_{12}N_2O_2$ (204): C, 64.70; H, 5.88; N, 13.72. Found: C, 64.65; H, 5.82; N, 13.66.

4-Methyl-2-[(5-methyl-3-isoxazolyl)amino]methylphenol (3b). This compound was obtained as brown crystals, yield 85%; mp 79–81°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.35 (s, 2H, —CH_2—), 5.50 (bs, 1H, NH, D_2O exchangeable), 5.70 (s, 1H, isoxazole-H), 7.00–7.50 (m, 3H, ArH), 10.05 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 219 ($M + H^+$); IR (KBr): 3500 (N—H), 3368 (O—H), 1605 (C=N), 1455 (C=C), 1065 cm^{-1} (C—O). *Anal*. Calcd. for $C_{12}H_{14}N_2O_2$ (218): C, 66.05; H, 6.42; N, 12.84. Found: C, 66.01; H, 5.98; N, 12.81.

4-Methoxy-2-[(5-methyl-3-isoxazolyl)amino]methylphenol (3c). This compound was obtained as brown crystals, yield 85%; mp 92–93°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 3.7 (s, 3H, CH_3), 4.00 (s, 2H, —CH_2—), 5.50 (bs, 1H, NH, D_2O exchangeable), 5.80 (s, 1H, isoxazole-H), 6.85–7.40 (m, 3H, ArH), 9.85 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 235 ($M + H^+$); IR (KBr): 3490 (N—H), 3350 (O—H), 1620 (C=N), 1460 (C=C), 1150 cm^{-1} (C—O). *Anal*. Calcd. for $C_{12}H_{14}N_2O_3$ (234): C, 61.53; H, 5.98; N, 11.96. Found: C, 61.88; H, 5.88; N, 11.85.

4-Chloro-2-[(5-methyl-3-isoxazolyl)amino]methylphenol (3d). This compound was obtained as brown crystals, yield 80%; mp 105–107°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 3.70 (s, 2H, —CH_2—), 4.50 (bs, 1H, NH, D_2O exchangeable), 6.02 (s, 1H, isoxazole-H), 7.00–7.50 (m, 3H, ArH), 10.02 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 239 ($M + H^+$); IR (KBr): 3550 (N—H), 3415 (O—H), 1630 (C=N), 1510 (C=C), 1205 cm^{-1} (C—O). *Anal*. Calcd. for $C_{11}H_{11}N_2O_2Cl$ (238): C, 55.46; H, 4.62; N, 11.76. Found: C, 55.50; H, 4.58; N, 11.80.

4-Bromo-2-[(5-methyl-3-isoxazolyl)amino]methylphenol (3e). This compound was obtained as brown crystals, yield 80%; mp 121–123°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H, CH_3), 3.95 (s, 2H, —CH_2—), 5.00 (bs, 1H, NH, D_2O exchangeable), 5.95 (s, 1H, isoxazole-H), 7.20–7.80 (m, 3H, ArH), 9.80 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 283 ($M + H^+$); IR (KBr): 3500 (N—H), 3395 (O—H), 1615 (C=N), 1560 (C=C), 1180 cm^{-1} (C—O). *Anal*. Calcd. for $C_{11}H_{11}N_2O_2Br$ (282): C, 46.80; H, 3.90; N, 9.92. Found: C, 46.95; H, 4.01; N, 9.85.

General procedure for the preparation of *N*-(2-hydroxybenzyl)-*N*-(5-methyl-3-isoxazolyl)-*N′*-phenylthioureas (4a–4f). To chloroform solution (15 mL) of amino methylphenols 3 (0.01 mol) arylisothio cyanate (0.01 mol) was slowly added with stirring. The reaction mixture was stirred at 90°C for 6 h. The solvent was removed by distillation under reduced pressure and the crude product was re-crystallized from ethanol.

N-(2-Hydroxybenzyl)-N-(5-methyl-3-isoxazolyl)-N′-phenylthiourea (4a). This compound was obtained as brown crystals, yield 85%; mp 100–102°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.01 (s, 1H, isoxazole-H), 6.8–7.8 (m, 9H, ArH), 8.52 (bs, 1H, NH, D_2O exchangeable), 9.42 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 340 ($M + H^+$); IR (KBr): 3239 (N—H), 3180 (O—H), 1641 (C=N), 1582, 1515 (C=C), 1225 cm^{-1} (C=S). *Anal*. Calcd. for $C_{18}H_{17}N_3O_2S$ (339): C, 63.71; H, 5.01; N, 12.38.Found: C, 63.59; H, 4.95; N, 12.35.

N′-(4-Chlorophenyl)-N-(2-hydroxybenzyl)-N-(5-methyl-3-isoxazolyl) thiourea (4b). This compound was obtained as brown crystals, yield 88%; mp 124–126°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 4.94 (s, 2H, CH_2), 5.96 (s, 1H, isoxazole-H), 7.01–7.82 (m, 8H, ArH), 8.80 (bs, 1H, NH, D_2O exchangeable), 9.50 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 374 ($M + H^+$); IR (KBr): 3300 (N—H), 3225 (O—H), 1640 (C=N), 1575 (C=C), 1230 cm^{-1} (C=S). *Anal*. Calcd. for $C_{18}H_{16}N_3O_2SCl$ (373): C, 57.90; H, 4.28; N, 11.26. Found: C, 57.86; H, 4.25; N, 11.29.

N′-(4-Bromophenyl)-N-(2-hydroxybenzyl)-N-(5-methyl-3-isoxazolyl) thiourea (4c). This compound was obtained as brown crystals, yield 80% mp 133–135°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 6.00 (s, 1H, isoxazole-H), 7.23–7.85 (m, 8H, ArH), 9.00 (bs, 1H, NH, D_2O exchangeable), 10.25 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 418 ($M + H^+$); *Anal*. Calcd. for $C_{18}H_{16}N_3O_2SBr$ (417): C, 51.79; H, 3.83; N, 10.07. Found: C, 51.82; H, 3.85; N, 9.98. IR (KBr): 3350 (N—H), 3200 (O—H), 1515 (C=C), 1225 cm^{-1} (C=S).

N-(2-Hydroxybenzyl)-N-(5-methyl-3-isoxazolyl)-N′-(4-methylphenyl) thiourea (4d). This was obtained as compound brown crystals, yield 85%; mp 120–122°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.75 (s, 2H, CH_2), 6.12 (s, 1H, isoxazole-H), 7.50–8.20 (m, 8H, ArH), 8.90 (bs, 1H, NH, D_2O exchangeable), 10.08 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 354 ($M + H^+$); IR

(KBr): 3329 (N—H), 3215 (O—H), 1510 (C=C), 1220 cm^{-1} (C=S). *Anal*. Calcd. for $C_{19}H_{19}N_3O_2S$ (353): C, 64.58; H, 5.38; N, 11.89. Found: C, 64.49; H, 5.32; N, 11.92.

N-(2-Hydroxy-5-methylbenzyl)-N-(5-methyl-3-isoxazolyl)-N′-phenylthiourea (4e). This compound was obtained as brown crystals, yield 88%; mp 136–138°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.66 (s, 2H, CH_2), 5.98 (s, 1H, isoxazole-H), 7.20–8.00 (m, 8H, ArH), 9.00 (bs, 1H, NH, D_2O exchangeable), 10.05 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 354 ($M + H^+$); IR (KBr): 3380 (N—H), 3290 (O—H), 1565 (C=C), 1235 cm^{-1} (C=S). *Anal*. Calcd. for $C_{19}H_{19}N_3O_2S$ (353): C, 64.58; H, 5.38; N, 11.89. Found: C, 64.55; H, 5.35; N, 11.95.

N-(2-Hydroxy-5-methoxybenzyl)-N-(5-methyl-3-isoxazolyl)-N′-phenylthiourea (4f). This compound was obtained as brown crystals, yield 80%; mp 127–129°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2), 6.20 (s, 1H, isoxazole-H), 7.00–7.85 (m, 8H, ArH), 8.98 (bs, 1H, NH, D_2O exchangeable), 9.80 (bs, 1H, OH, D_2O exchangeable). EI-MS: *m/z* 370 ($M + H^+$); IR (KBr): 3375 (N—H), 3185 (O—H), 1560 (C=C), 1215 cm^{-1} (C=S). *Anal*. Calcd. for $C_{19}H_{19}N_3O_2S$ (369): C, 61.78; H, 5.14; N, 11.38. Found: C, 61.82; H, 5.08; N, 11.35.

General procedure for the preparation of 5-(5-methylisoxazol-3-yl)-3-aryl-3,4,5,6-tetrahydro-2*H*-1,3,5-benzoxadiazocine-4-thiones (5a–5f). To an ethanolic solution (15 mL) of thioureas 4 (0.01 mol), Formaldehyde (0.01 mol) was slowly added with stirring. The mixture was refluxed for 6–8 h (Monitored with TLC). The gummy product obtained, after the removal of solvent, was processed with pet ether. The product was purified by re-crystallization from ethanol.

5-(5-Methyl-3-isoxazolyl)-3-phenyl-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5a). This compound was obtained as pale brown crystals, yield 90%; mp 128–129°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 5.88 (s, 2H, CH_2), 6.02 (s, 1H, isoxazole-H), 7.02–7.65 (m, 9H, ArH). EI-MS: *m/z* 352 ($M + H^+$); IR (KBr): 1610 (C=N), 1220 cm^{-1} (C=S). *Anal*. Calcd. for $C_{19}H_{17}N_3O_2S$ (351): C, 64.95; H, 4.84; N, 11.96. Found: C, 65.01; H, 4.82; N, 11.92.

3-(4-Chlorophenyl)-5-(5-methyl-3-isoxazolyl)-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5b). This compound was obtained as pale brown crystals, yield 85%; mp 145–147°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H, CH_3), 4.62 (s, 2H, CH_2), 6.00 (s, 2H, CH_2), 6.20 (s, 1H, isoxazole-H), 7.23–7.85 (m, 8H, ArH). EI-MS: *m/z* 386 ($M + H^+$); IR (KBr): 1625 (C=N), 1210 cm^{-1} (C=S). *Anal*. Calcd. for $C_{19}H_{16}N_3O_2SCl$ (385): C, 59.22; H, 4.15; N, 10.90. Found: C, 59.17; H, 4.10; N, 11.00.

3-(4-Bromophenyl)-5-(5-methyl-3-isoxazolyl)-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5c). This compound was obtained as pale brown crystals, yield 85%; mp 160–162°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H, CH_3), 4.80 (s, 2H, CH_2), 6.05 (s, 2H, CH_2), 6.25 (s, 1H, isoxazole-H), 7.50–7.88 (m, 8H, ArH). EI-MS: *m/z* 430 ($M + H^+$); IR (KBr): 1600 (C=N), 1202 cm^{-1} (C=S). *Anal*. Calcd. for $C_{19}H_{16}N_3O_2SBr$ (429): C, 53.14; H, 3.72; N, 9.79. Found: C, 53.09; H, 3.70; N, 9.75.

5-(5-Methyl-3-isoxazolyl)-3-(4-methylphenyl)-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5d). This compound was obtained as pale brown crystals, yield 88%; mp 140–142°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.75 (s, 2H, CH_2), 5.85 (s, 2H, CH_2), 6.05 (s, 1H, isoxazole-H), 7.25–7.98 (m, 8H, ArH). EI-MS: *m/z* 366 ($M + H^+$); IR (KBr): 1618 (C=N), 1215 cm^{-1} (C=S). *Anal*. Calcd. for $C_{20}H_{19}N_3O_2S$ (365): C, 65.75; H, 5.20; N, 11.50. Found: C, 65.81; H, 5.15; N, 11.48.

8-Methyl-5-(5-methyl-3-isoxazolyl)-3-phenyl-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5e). This compound was obtained as pale brown crystals, yield 80%; mp 155–157°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 5.80 (s, 2H, CH_2), 6.02 (s, 1H, isoxazole-H), 7.00–7.65 (m, 8H, ArH). EI-MS: *m/z* 366 ($M + H^+$); IR (KBr): 1610 (C=N), 1225 cm^{-1} (C=S). *Anal*. Calcd. for $C_{20}H_{19}N_3O_2S$ (365): C, 65.75; H, 5.20; N, 11.50. Found: C, 65.70; H, 5.22; N, 11.47.

8-Methoxy-5-(5-methyl-3-isoxazolyl)-3-phenyl-3,4,5,6-tetrahydro-2H-1,3,5-benzoxadiazocine-4-thione (5f). This compound was obtained as pale brown crystals, yield 80%; mp 165–167°C, ^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.80 (s, 2H, CH_2), 6.00 (s, 2H, CH_2), 6.15 (s, 1H, isoxazole-H), 7.00–7.50 (m, 8H, ArH). EI-MS: *m/z* 382 ($M + H^+$); IR (KBr): 1625 (C=N), 1235 cm^{-1} (C=S). *Anal*. Calcd. for $C_{20}H_{19}N_3O_3S$ (381): C, 62.99; H, 4.98; N, 11.02. Found: C, 63.05; H, 5.01; N, 11.00.

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