

HETEROCYCLES, Vol. 89, No. 4, 2014, pp. 1041 - 1053. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 9th January, 2014, Accepted, 30th January, 2014, Published online, 10th February, 2014
DOI: 10.3987/COM-14-12938

REINVESTIGATION OF 1,3,4-THIADIAZOL-2(3*H*)-IMINIUM BROMIDE IN THE TWO-STEP SYNTHESIS OF IMIDAZO[2,1-*b*][1,3,4]- THIADIAZOLES

Shigeki Sano,* Keisuke Matsuura, Hayato Sumiyoshi, Akira Miki, Syuji
Kitaike, and Michiyasu Nakao

Graduate School of Pharmaceutical Sciences, The University of Tokushima,
Sho-machi, Tokushima 770-8505, Japan

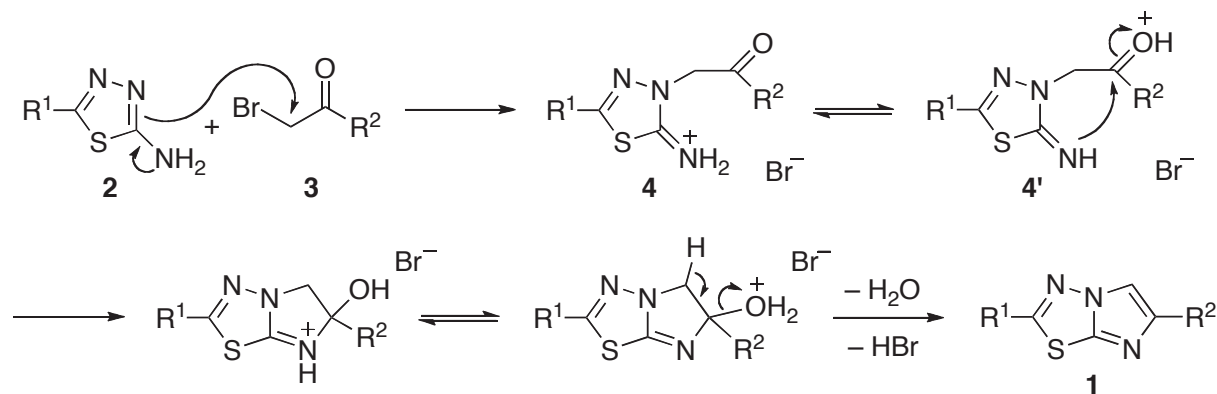
E-mail: ssano@tokushima-u.ac.jp

Abstract – The synthesis of 1,3,4-thiadiazol-2(3*H*)-iminium bromides, which are intermediates in the most commonly used synthetic approach to imidazo[2,1-*b*][1,3,4]thiadiazoles, and a single crystal X-ray diffraction study of one of these iminium bromides are described. Cyclization of the resulting 1,3,4-thiadiazol-2(3*H*)-iminium bromides under microwave irradiation afforded imidazo[2,1-*b*][1,3,4]thiadiazoles in 80-100% yields.

Imidazo[2,1-*b*][1,3,4]thiadiazoles are an important class of fused heterocyclic compounds that have attracted attention due to their diverse range of biological activities.¹ Indeed, these compounds have been shown to possess crucial effects such as anticancer,^{2,3} antibacterial,⁴⁻⁷ antitubercular,^{3,5,8} antifungal,^{6,7,9,10} antimicrobial,^{3,7,10,11} analgesic,^{7,12} anticonvulsant¹² and antihyperlipidemic¹³ activities. In addition, anti-inflammatory,^{10,14} antisecretory,¹⁵ antiapoptotic,¹⁶ anthelmintic,¹⁷ diuretic,¹⁸ leishmanicidal,¹⁹ cardiogenic,²⁰ and herbicidal²¹ effects have also been reported. Thus, the imidazo[2,1-*b*][1,3,4]thiadiazoles are thought to have tremendous potential in medicinal chemistry.

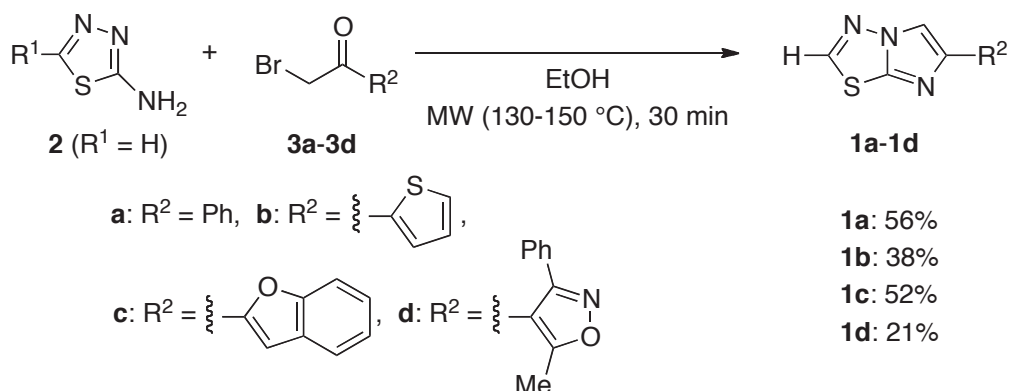
Recently, a novel method for synthesizing imidazo[2,1-*b*][1,3,4]thiadiazoles by the reaction of 4,5-disubstituted-*N*-arylaminoimidazole-2-thiones with isocyanides in the presence of azodicarboxylates has been reported.²² However, the most commonly used method for the preparation of imidazo[2,1-*b*][1,3,4]thiadiazole **1** is the one-pot reaction of 5-substituted-2-amino-1,3,4-thiadiazole **2** with appropriate α -haloketone **3**. Since 1952, beginning with the work of two-step synthesis of **1** by Matsukawa and Ban,²³ numerous studies on the reaction of **2** and **3** have been reported. A plausible mechanism involving a 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4** for the one-pot synthesis is outlined in

Scheme 1. Modified synthetic methods based on the reaction of **2** and **3** have recently been reported by various authors.²⁴ However, these reactions have not necessarily been optimized to furnish a variety of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives. In this context, we planned to reinvestigate the two-step reactions of **2** and **3** for the preparation of imidazo[2,1-*b*][1,3,4]thiadiazole **1**.



Scheme 1. Plausible mechanism for the formation of imidazo[2,1-*b*][1,3,4]thiadiazole **1**

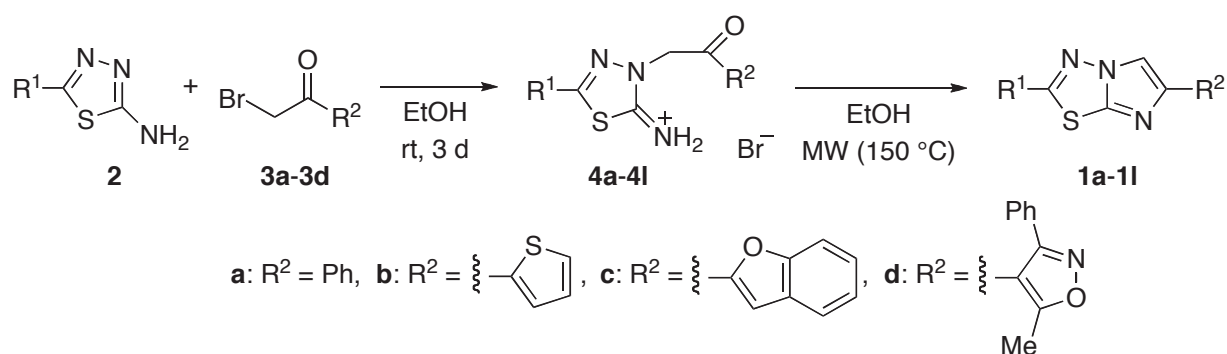
First, we synthesized imidazo[2,1-*b*][1,3,4]thiadiazoles **1a-1d** utilizing an ordinary one-pot synthetic method. Thus, a mixture of 2-amino-1,3,4-thiadiazole **2** ($R^1 = H$) and 1 mol eq. of α -haloketone **3** [$R^2 = Ph$, 2-thiophenyl, 2-benzofuranyl, and 4-(5-methyl-3-phenylisoxazolyl)] underwent a known reaction under microwave irradiation²⁵ with a single-mode microwave reactor (InitiatorTM 60; Biotage AB) at 130-150 °C to afford imidazo[2,1-*b*][1,3,4]thiadiazoles **1a-1d** in 21-56% yields (Scheme 2). The competition between cyclization and decomposition of 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4** at elevated reaction temperatures may be responsible for the lower chemical yields of imidazo[2,1-*b*][1,3,4]thiadiazole **1**.



Scheme 2. One-pot synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles **1a-1d**

We therefore investigated an effective preparation of 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4**, which is the intermediate in the ordinary one-pot synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole **1** utilizing

2-amino-1,3,4-thiadiazole **2** and α -haloketone **3**. As a result, the reaction of **2** ($R^1 = \text{H, Me, and Et}$) and 1 mol eq. of **3** [$R^2 = \text{Ph, 2-thiophenyl, 2-benzofuranyl, and 4-(5-methyl-3-phenylisoxazolyl)}$] in ethanol at ambient temperature furnished 1,3,4-thiadiazol-2(3*H*)-iminium bromides **4a-4l** in 54-87% yields (Scheme 3, Table 1). The structures of **4a-4l** were established by spectroscopic methods. Cyclization of 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4** to imidazo[2,1-*b*][1,3,4]thiadiazole **1** did not occur under these reaction conditions. Unfortunately, the chemical yields of **4** were lower than expected. The solubility of this compound in organic solvents, which was dependent on substituents R^1 and R^2 , may be one reason for the disappointing yields. However, the structure of **4l** was confirmed for the first time by a single crystal X-ray diffraction study (an ORTEP view of a single molecule of **4l** is given in Figure 1).²⁶



Scheme 3. Two-step synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles **1a-1l**

Table 1. Synthesis of 1,3,4-thiadiazol-2(3*H*)-iminium bromides **4a-4l**

Entry	R^1	R^2	Yield (%) ^a
1	H	a	77 (4a)
2	H	b	54 (4b)
3	H	c	61 (4c)
4	H	d	68 (4d)
5	Me	a	76 (4e)
6	Me	b	66 (4f)
7	Me	c	79 (4g)
8	Me	d	70 (4h)
9	Et	a	74 (4i)
10	Et	b	69 (4j)
11	Et	c	73 (4k)
12	Et	d	87 (4l)

^a Isolated yields.

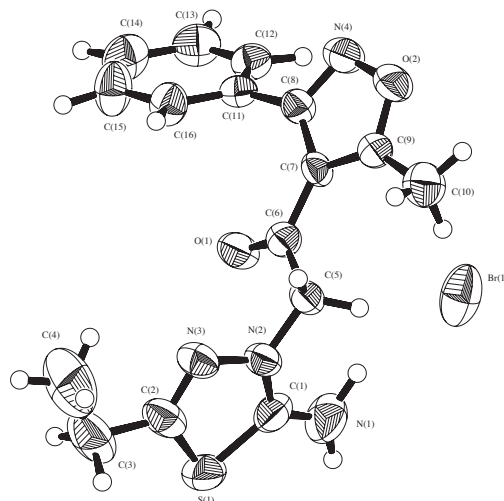


Figure 1. ORTEP drawing of 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4I**

Having identified suitable conditions for the preparation of 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4**, we optimized the cyclization reaction of **4** to imidazo[2,1-*b*][1,3,4]thiadiazole **1** with the use of a single-mode microwave reactor (InitiatorTM 60; Biotage AB). The cyclization of 1,3,4-thiadiazol-2(3*H*)-iminium bromides **4a-4I** under microwave irradiation at 150 °C in ethanol consequently afforded the desired cyclized compounds **1a-1I** in excellent yields (Scheme 3, Table 2). The structures of **1a-1I** were determined by spectroscopic methods. In addition, the structure of **1I** was independently established by a single crystal X-ray diffraction study as shown in Figure 2.²⁷

Table 2. Synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles **1a-1I**

Entry	R ¹	R ²	Time (min)	Yield (%) ^a
1	H	a	4	100 (1a)
2	H	b	30	80 (1b)
3	H	c	5	92 (1c)
4	H	d	5	100 (1d)
5	Me	a	5	100 (1e)
6	Me	b	10	100 (1f)
7	Me	c	20	99 (1g)
8	Me	d	7	93 (1h)
9	Et	a	5	100 (1i)
10	Et	b	10	91 (1j)
11	Et	c	20	100 (1k)
12	Et	d	5	94 (1I)

^a Isolated yields.

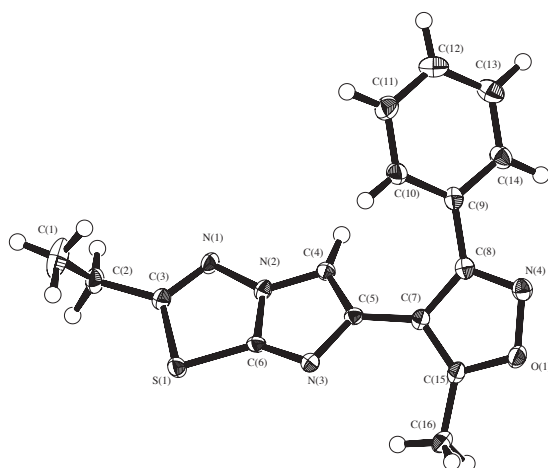


Figure 2. ORTEP drawing of imidazo[2,1-*b*][1,3,4]thiadiazole **11**

In this work, we have described the preparation of 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4** in ethanol and the first example of the single crystal X-ray crystallography of one of these intermediates. The cyclization of 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4** is general with respect to all examples and the products, imidazo[2,1-*b*][1,3,4]thiadiazole **1**, were obtained in excellent yields within minutes under microwave irradiation. Further investigations to provide more useful insight into the efficient preparation of 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4** are currently underway.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-6200 IR Fourier transform spectrometer. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Bruker AV500 spectrometers, respectively. Chemical shifts are given in δ values (parts per million) using tetramethylsilane (TMS) as an internal standard. Electron spray ionization mass spectra (ESIMS) were recorded on a Waters LCT Premier spectrometer. Elemental combustion analyses were performed using a Yanagimoto CHN CORDER MT-5 and a J-SCIENCE LAB JM10. Microwave-assisted reaction was performed utilizing automated single-mode microwave synthesizer (InitiatorTM 60; Biotage AB). X-Ray crystallographic analysis was performed using a Rigaku RAXIS-RAPID diffractometer. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F₂₅₄). Column chromatography was carried out on silica gel [Fuji Silysia Chemical PSQ 60B (spherical)]. All reagents were used as purchased.

Typical Procedure for Preparation of 1,3,4-Thiadiazol-2(3*H*)-iminium Bromide **4**

A solution of 2-amino-5-ethyl-1,3,4-thiadiazole **2** ($\text{R}^1 = \text{H}$) (129 mg, 1 mmol) and **3d** (280 mg, 1 mmol) in EtOH (5 mL) was stirred at rt for 3 days. The reaction mixture was then evaporated *in vacuo* to afford a

crude product, which was purified by column chromatography on silica gel [CHCl_3 —MeOH (20:1)] to give **4l** (355 mg, 87%) as a pale yellow solid.

3-(2-Oxo-2-phenylethyl)-1,3,4-thiadiazol-2(3H)-iminium Bromide (4a)²³ Colorless solid; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 6.11 (s, 2H), 7.60–7.68 (m, 2H), 7.74–7.81 (m, 1H), 8.02–8.09 (m, 2H), 9.02 (s, 1H), 9.96 (brs, 2H); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ 57.3, 128.3, 128.8, 133.5, 134.4, 145.1, 167.9, 190.1; IR (KBr) 3004, 1635, 1566, 1448, 1418, cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{10}\text{H}_{10}\text{N}_3\text{OS}$ $[\text{M-Br}]^+$, 220.0545; found, 220.0535. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{BrN}_3\text{OS}$: C, 40.1; H, 3.36; N, 14.00. Found: C, 40.03; H, 3.53; N, 13.99%.

3-[2-Oxo-2-(thiophen-2-yl)ethyl]-1,3,4-thiadiazol-2(3H)-iminium Bromide (4b) Yellow plate (MeOH); ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 6.01 (s, 2H), 7.38 (dd, $J = 3.9, 4.8$ Hz, 1H), 8.18 (dd, $J = 1.0, 3.8$ Hz, 1H), 8.20 (dd, $J = 0.9, 4.9$ Hz, 1H), 9.00 (s, 1H), 9.96 (brs, 2H); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ 56.6, 129.1, 135.1, 136.5, 139.4, 145.0, 168.1, 183.2; IR (KBr) 2994, 1670, 1627, 1562, 1520, 1408, 1249, 1066 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_8\text{H}_8\text{N}_3\text{OS}_2$ $[\text{M-Br}]^+$, 226.0109; found, 226.0093. Anal. Calcd for $\text{C}_8\text{H}_8\text{BrN}_3\text{OS}_2$: C, 31.38; H, 2.63; N, 13.72. Found: C, 31.29; H, 2.74; N, 13.61%.

3-[2-(Benzofuran-2-yl)-2-oxoethyl]-1,3,4-thiadiazol-2(3H)-iminium Bromide (4c) Pale red needle (MeOH—THF); ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 6.01 (s, 2H), 7.41–7.48 (m, 1H), 7.59–7.67 (m, 1H), 7.78–7.84 (m, 1H), 7.91–7.97 (m, 1H), 8.14 (d, $J = 0.7$ Hz, 1H), 9.03 (s, 1H), 9.96 (brs, 2H); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ 56.6, 112.3, 115.8, 123.9, 124.4, 126.3, 129.2, 145.2, 149.3, 155.0, 168.1, 180.8; IR (KBr) 2997, 1686, 1627, 1561, 1417, 1343, 1287, 1171, 1142, 1112, 1025 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{12}\text{H}_{10}\text{N}_3\text{O}_2\text{S}$ $[\text{M-Br}]^+$, 260.0494; found, 260.0516. Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{BrN}_3\text{O}_2\text{S}$: C, 42.37; H, 2.96; N, 12.35. Found: C, 42.16; H, 3.10; N, 12.37%.

3-[2-(5-Methyl-3-phenylisoxazol-4-yl)-2-oxoethyl]-1,3,4-thiadiazol-2(3H)-iminium Bromide (4d) Colorless solid; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 2.89 (s, 3H), 5.53 (s, 2H), 7.45–7.61 (m, 5H), 8.95 (s, 1H), 9.86 (brs, 2H); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ 14.3, 58.7, 113.9, 127.9, 128.3, 129.1, 123.0, 144.9, 161.9, 167.8, 176.2, 184.0; IR (KBr) 3023, 1698, 1561, 1416, 1291, 1228, 1139, 1075 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{14}\text{H}_{13}\text{N}_4\text{O}_2\text{S}$ $[\text{M-Br}]^+$, 301.0759; found, 301.0764.

5-Methyl-3-(2-oxo-2-phenylethyl)-1,3,4-thiadiazol-2(3H)-iminium Bromide (4e)²³ Colorless solid; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 2.58 (s, 3H), 6.03 (s, 2H), 7.60–7.68 (m, 2H), 7.74–7.80 (m, 1H), 8.01–8.08 (m, 2H), 9.90 (brs, 2H); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ 15.8, 57.1, 128.3, 128.9, 133.5,

134.4, 154.1, 168.4, 190.1; IR (KBr) 3001, 1689, 1582, 1552, 1447, 1411, 1347, 1238, 1123 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{11}\text{H}_{12}\text{N}_3\text{OS} [\text{M}-\text{Br}]^+$, 234.0701; found, 234.0683. Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{BrN}_3\text{OS}$: C, 42.05; H, 3.85; N, 13.37. Found: C, 41.75; H, 3.91; N, 13.54%.

5-Methyl-3-[2-oxo-2-(thiophen-2-yl)ethyl]-1,3,4-thiadiazol-2(3H)-iminium Bromide (4f) Brown solid; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 2.56 (s, 3H), 5.94 (s, 2H), 7.38 (dd, $J = 3.9, 4.8$ Hz, 1H), 8.18 (dd, $J = 1.0, 3.8$ Hz, 1H), 8.21 (dd, $J = 1.0, 4.9$ Hz, 1H), 9.93 (brs, 2H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ 15.8, 56.4, 129.1, 135.1, 136.5, 139.4, 154.2, 168.6, 183.2; IR (KBr) 2997, 1667, 1632, 1554, 1520, 1412, 1254, 1068 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_9\text{H}_{10}\text{N}_3\text{OS}_2 [\text{M}-\text{Br}]^+$, 240.0265; found, 240.0243. Anal. Calcd for $\text{C}_9\text{H}_{10}\text{BrN}_3\text{OS}_2$: C, 33.76; H, 3.15; N, 13.12. Found: C, 33.60; H, 3.30; N, 13.00%.

3-[2-(Benzofuran-2-yl)-2-oxoethyl]-5-methyl-1,3,4-thiadiazol-2(3H)-iminium Bromide (4g) Colorless solid; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 2.58 (s, 3H), 5.97 (s, 2H), 7.41–7.48 (m, 1H), 7.60–7.66 (m, 1H), 7.79–7.84 (m, 1H), 7.91–7.97 (m, 1H), 8.15 (s, 1H), 10.03 (brs, 2H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ 15.8, 56.3, 112.3, 115.8, 124.0, 124.4, 126.4, 129.2, 149.3, 154.3, 155.0, 168.6, 180.8; IR (KBr) 2992, 1684, 1632, 1556, 1411, 1343, 1287, 1175, 1143, 1029 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{13}\text{H}_{12}\text{N}_3\text{O}_2\text{S} [\text{M}-\text{Br}]^+$, 274.0650; found, 274.0655. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{BrN}_3\text{O}_2\text{S}$: C, 44.08; H, 3.41; N, 11.86. Found: C, 43.86; H, 3.69; N, 11.64%.

5-Methyl-3-[2-(5-methyl-3-phenylisoxazol-4-yl)-2-oxoethyl]-1,3,4-thiadiazol-2(3H)-iminium Bromide (4h) Colorless needle (MeOH); ^1H NMR (500 MHz, CDCl_3) δ 2.34 (s, 3H), 2.77 (s, 3H), 4.81 (s, 2H), 7.49–7.59 (m, 3H), 7.59–7.68 (m, 2H), 8.13 (brs, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1, 16.8, 57.0, 115.0, 128.5, 129.0, 129.3, 130.4, 147.6, 161.4, 165.2, 176.6, 186.7; IR (KBr) 2925, 1694, 1570, 1416, 1292, 1231, 1138, 1075 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{15}\text{H}_{15}\text{N}_4\text{O}_2\text{S} [\text{M}-\text{Br}]^+$, 315.0916; found, 315.0917. Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{BrN}_4\text{O}_2\text{S}$: C, 45.58; H, 3.82; N, 14.17. Found: C, 45.43; H, 3.85; N, 14.05%.

5-Ethyl-3-(2-oxo-2-phenylethyl)-1,3,4-thiadiazol-2(3H)-iminium Bromide (4i)²³ Colorless needle (MeOH); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 1.25 (t, $J = 7.5$ Hz, 3H), 2.94 (q, $J = 7.5$ Hz, 2H), 6.00 (s, 2H), 7.60–7.66 (m, 2H), 7.74–7.80 (m, 1H), 8.02–8.07 (m, 2H), 9.82 (brs, 2H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ 12.1, 23.3, 57.1, 128.3, 128.9, 133.5, 134.4, 159.2, 168.2, 190.1; IR (KBr) 2995, 1687, 1580, 1548, 1448, 1409, 1345, 1233, 1122 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{NaOS} [\text{M}-\text{HBr}+\text{Na}]^+$, 270.0677; found, 270.0665. Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{BrN}_3\text{OS}$: C, 43.91; H, 4.30; N, 12.80. Found: C, 43.71; H, 4.23; N, 12.69%.

5-Ethyl-3-[2-oxo-2-(thiophen-2-yl)ethyl]-1,3,4-thiadiazol-2(3H)-iminium Bromide (4j) Colorless solid; ^1H NMR (500 MHz, DMSO- d_6) δ 1.23 (t, $J = 7.5$ Hz, 3H), 2.94 (q, $J = 7.5$ Hz, 2H), 5.95 (s, 2H), 7.38 (dd, $J = 3.9, 4.9$ Hz, 1H), 8.18 (dd, $J = 1.0, 3.9$ Hz, 1H), 8.21 (dd, $J = 1.0, 4.9$ Hz, 1H), 9.93 (brs, 2H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 12.1, 23.3, 56.5, 129.1, 135.1, 136.5, 139.4, 159.3, 168.3, 183.2; IR (KBr) 2989, 1676, 1630, 1552, 1515, 1408, 1250, 1066 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{NaOS}_2$ [$\text{M}-\text{HBr}+\text{Na}$] $^+$, 276.0241; found, 276.0267. Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{BrN}_3\text{OS}_2$: C, 35.93; H, 3.62; N, 12.57. Found: C, 35.68; H, 3.78; N, 12.54%.

3-[2-(Benzofuran-2-yl)-2-oxoethyl]-5-ethyl-1,3,4-thiadiazol-2(3H)-iminium Bromide (4k) Colorless solid; ^1H NMR (500 MHz, DMSO- d_6) δ 1.25 (t, $J = 7.5$ Hz, 3H), 2.95 (q, $J = 7.5$ Hz, 2H), 5.94 (s, 2H), 7.41–7.47 (m, 1H), 7.60–7.66 (m, 1H), 7.78–7.84 (m, 1H), 7.91–7.96 (m, 1H), 8.13 (d, $J = 0.8$ Hz, 1H), 9.93 (brs, 2H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 12.1, 23.3, 56.4, 112.3, 115.8, 123.9, 124.4, 126.4, 129.2, 149.3, 155.0, 159.4, 168.4, 180.8; IR (KBr) 2979, 1685, 1633, 1552, 1413, 1347, 1290, 1176, 1144, 1115, 1031 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}_2\text{S}$ [$\text{M}-\text{Br}$] $^+$, 288.0807; found, 288.0821. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{BrN}_3\text{O}_2\text{S}$: C, 45.66; H, 3.83; N, 11.41. Found: C, 45.39; H, 3.66; N, 11.43%.

5-Ethyl-3-[2-(5-methyl-3-phenylisoxazol-4-yl)-2-oxoethyl]-1,3,4-thiadiazol-2(3H)-iminium Bromide (4l) Colorless column (MeOH); ^1H NMR (500 MHz, CDCl_3) δ 1.29 (t, $J = 7.6$ Hz, 3H), 2.79 (q, $J = 7.5$ Hz, 2H), 2.80 (s, 3H), 5.23 (s, 2H), 7.51–7.57 (m, 3H), 7.69–7.75 (m, 2H), 9.87 (brs, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 12.3, 14.5, 24.1, 59.6, 114.6, 128.1, 129.0, 129.6, 130.5, 159.8, 161.4, 168.3, 177.3, 183.9; IR (KBr) 2979, 1695, 1633, 1579, 1417, 1292 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{16}\text{H}_{17}\text{N}_4\text{O}_2\text{S}$ [$\text{M}-\text{Br}$] $^+$, 329.1072; found, 329.1043.

Typical Procedure for Preparation of Imidazo[2,1-*b*][1,3,4]thiadiazole 1

A solution of **4a** (30 mg, 0.1 mmol) in EtOH (0.5 mL) was irradiated at 150 °C for 4 min utilizing a Biotage Initiator[®] microwave synthesizer. After being concentrated *in vacuo*, the residue was treated with 0.2N Na_2CO_3 aq (0.5 mL) and then extracted with CHCl_3 (30 mL x 2). The extract was dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo* to afford **1a** (20 mg, 100%) as a pale orange solid.

6-Phenylimidazo[2,1-*b*][1,3,4]thiadiazole (1a)^{23,28} Orange needle (EtOH), mp 128.5–129.0 °C (lit.,^{23,28} 130–132 °C); ^1H NMR (500 MHz, CDCl_3) δ 7.29–7.34 (m, 1H), 7.39–7.45 (m, 2H), 7.81–7.86 (m, 2H), 8.10 (s, 1H), 8.52 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 109.5, 125.2, 127.7, 128.7, 133.8, 144.3, 146.4, 147.6; IR (KBr) 3138, 3055, 1490, 1439, 1336, 1255, 1168, 1070 cm^{-1} ; ESI-MS m/z : calcd for $\text{C}_{10}\text{H}_8\text{N}_3\text{S}$ [$\text{M}+\text{H}$] $^+$, 202.0439; found, 202.0443. Anal. Calcd for $\text{C}_{10}\text{H}_7\text{N}_3\text{S}$: C, 59.68; H, 3.51; N, 20.88. Found: C,

59.64; H, 3.64; N, 20.76%.

6-(Thiophen-2-yl)imidazo[2,1-*b*][1,3,4]thiadiazole (1b) Colorless needle (CHCl₃–*n*-hexane), mp 124.0–125.0 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.07 (dd, *J* = 3.6, 5.1 Hz, 1H), 7.27 (dd, *J* = 1.1, 5.1 Hz, 1H), 7.34 (dd, *J* = 1.1, 3.6 Hz, 1H), 8.01 (s, 1H), 8.51 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 108.9, 122.9, 124.6, 127.7, 137.3, 142.6, 144.2, 146.5; IR (KBr) 3142, 3062, 1800, 1476, 1363, 1318, 1258, 1208, 1159, 1017 cm⁻¹; ESI-MS *m/z*: calcd for C₈H₆N₃S₂ [M+H]⁺, 208.0003; found, 208.0015.

6-(Benzofuran-2-yl)imidazo[2,1-*b*][1,3,4]thiadiazole (1c) Brown needle (EtOH), mp 188.0–190.0 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.12 (d, *J* = 0.7 Hz, 1H), 7.21–7.32 (m, 2H), 7.49–7.54 (m, 1H), 7.58–7.63 (m, 1H), 8.22 (s, 1H), 8.57 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 102.1, 110.9, 111.1, 121.0, 123.0, 124.4, 128.9, 139.3, 145.1, 147.1, 150.9, 154.6; IR (KBr) 3093, 1632, 1486, 1444, 1258, 1171, 1058 cm⁻¹; ESI-MS *m/z*: calcd for C₁₂H₇N₃NaOS [M+Na]⁺, 264.0208; found, 264.0195.

4-(Imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)-5-methyl-3-phenylisoxazole (1d) Yellow needle (EtOH), mp 178.0–179.0 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.68 (s, 3H), 7.38–7.48 (m, 3H), 7.49 (s, 1H), 7.57–7.62 (m, 2H), 8.53 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 12.3, 109.4, 112.2, 128.6, 128.7, 129.3, 129.6, 137.4, 143.8, 146.7, 161.3, 168.2; IR (KBr) 3159, 3111, 2921, 1640, 1487, 1226, 1168 cm⁻¹; ESI-MS *m/z*: calcd for C₁₄H₁₀N₄NaOS [M+Na]⁺, 305.0473; found, 305.0455. Anal. Calcd for C₁₄H₁₀N₄OS: C, 59.56; H, 3.57; N, 19.85. Found: C, 59.43; H, 3.82; N, 19.56%.

2-Methyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole (1e)^{28,29} Yellow plate (EtOH), mp 140.0–141.0 °C (lit.,²⁸ 135–137 °C, lit.,²⁹ 137–139 °C); ¹H NMR (500 MHz, CDCl₃) δ 2.71 (s, 3H), 7.26–7.31 (m, 1H), 7.38–7.43 (m, 2H), 7.79–7.83 (m, 2H), 7.96 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 17.8, 109.1, 125.0, 127.5, 128.7, 134.0, 145.7, 146.1, 159.2; IR (KBr) 3117, 1604, 1478, 1258, 1200, 1062 cm⁻¹; ESI-MS *m/z*: calcd for C₁₁H₉N₃NaS [M+Na]⁺, 238.0415; found, 238.0408. Anal. Calcd for C₁₁H₉N₃S: C, 61.37; H, 4.21; N, 19.52. Found: C, 61.27; H, 4.13; N, 19.48%.

2-Methyl-6-(thiophen-2-yl)imidazo[2,1-*b*][1,3,4]thiadiazole (1f) Yellow column (EtOH), mp 169.0–170.0 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.71 (s, 3H), 7.06 (dd, *J* = 3.6, 5.0 Hz, 1H), 7.25 (dd, *J* = 1.1, 5.1 Hz, 1H), 7.32 (dd, *J* = 1.1, 3.6 Hz, 1H), 7.87 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 17.8, 108.5, 122.5, 124.2, 127.6, 137.6, 141.0, 145.5, 159.4; IR (KBr) 3142, 3060, 2918, 1796, 1542, 1476, 1268, 1196, 1045 cm⁻¹; ESI-MS *m/z*: calcd for C₉H₈N₃S₂ [M+H]⁺, 222.0160; found, 222.0170. Anal. Calcd for C₉H₇N₃S₂: C, 48.85; H, 3.19; N, 18.99. Found: C, 48.69; H, 3.28; N, 18.84%.

6-(Benzofuran-2-yl)-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole (1g)³⁰ Orange needle (EtOH), mp 178.0–179.0 °C (lit.,³⁰ >250 °C); ¹H NMR (500 MHz, CDCl₃) δ 2.74 (s, 3H), 7.07 (d, *J* = 0.7 Hz, 1H), 7.21–7.30 (m, 2H), 7.48–7.52 (m, 1H), 7.57–7.61 (m, 1H), 8.09 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 17.9, 101.5, 110.6, 111.0, 120.9, 123.0, 124.2, 129.0, 137.8, 146.5, 151.2, 154.6, 160.0; IR (KBr) 3142, 1632, 1444, 1255, 1171, 1063 cm⁻¹; ESI-MS *m/z*: calcd for C₁₃H₉N₃NaOS [M+Na]⁺, 278.0364; found, 278.0354. Anal. Calcd for C₁₃H₉N₃OS: C, 61.16; H, 3.55; N, 16.46. Found: C, 61.02; H, 3.71; N, 16.21%.

5-Methyl-4-(2-methylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)-3-phenylisoxazole (1h) Colorless needle (EtOH), mp 174.5–175.5 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.66 (s, 3H), 2.70 (s, 3H), 7.35 (s, 1H), 7.37–7.48 (m, 3H), 7.55–7.63 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 12.3, 17.8, 109.5, 111.9, 128.5, 128.7, 129.3, 129.5, 135.7, 145.2, 159.6, 161.2, 168.0; IR (KBr) 3113, 1637, 1468, 1277, 1194, 1055 cm⁻¹; ESI-MS *m/z*: calcd for C₁₅H₁₂N₄NaOS [M+Na]⁺, 319.0630; found, 319.0632.

2-Ethyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole (1i)²³ Colorless plate (EtOH); mp 129.0–130.0 °C (lit.,²³ 127–128 °C); ¹H NMR (500 MHz, CDCl₃) δ 1.44 (t, *J* = 7.6 Hz, 3H), 3.03 (q, *J* = 7.6 Hz, 2H), 7.26–7.31 (m, 1H), 7.38–7.43 (m, 2H), 7.79–7.84 (m, 2H), 7.96 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 12.9, 25.7, 109.1, 125.0, 127.4, 128.7, 134.0, 145.3, 146.0, 165.7; IR (KBr) 3139, 2964, 1605, 1526, 1478, 1192 cm⁻¹; ESI-MS *m/z*: calcd for C₁₂H₁₂N₃S [M+H]⁺, 230.0752; found, 230.0752. Anal. Calcd for C₁₂H₁₁N₃S: C, 62.86; H, 4.84; N, 18.33. Found: C, 62.85; H, 4.90; N, 18.35%.

2-Ethyl-6-(thiophen-2-yl)imidazo[2,1-*b*][1,3,4]thiadiazole (1j) Colorless needle (EtOH), mp 124.0–125.5 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.43 (t, *J* = 7.6 Hz, 3H), 3.03 (q, *J* = 7.6 Hz, 2H), 7.06 (dd, *J* = 3.6, 5.1 Hz, 1H), 7.25 (dd, *J* = 1.1, 5.1 Hz, 1H), 7.32 (dd, *J* = 1.1, 3.6 Hz, 1H), 7.87 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 13.0, 25.7, 108.5, 122.5, 124.1, 127.6, 137.7, 141.0, 145.2, 165.9; IR (KBr) 3138, 3064, 1791, 1465, 1268, 1198, 1049 cm⁻¹; ESI-MS *m/z*: calcd for C₁₀H₁₀N₃S₂ [M+H]⁺, 236.0316; found, 236.0302. Anal. Calcd for C₁₀H₉N₃S₂: C, 51.04; H, 3.85; N, 17.86. Found: C, 50.94; H, 4.06; N, 17.56%.

6-(Benzofuran-2-yl)-2-ethylimidazo[2,1-*b*][1,3,4]thiadiazole (1k) Brown needle (EtOH), mp 129.0–130.0 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.46 (t, *J* = 7.6 Hz, 3H), 3.05 (q, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 0.7 Hz, 1H), 7.20–7.30 (m, 2H), 7.47–7.53 (m, 1H), 7.57–7.62 (m, 1H), 8.08 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 12.9, 25.8, 101.5, 110.6, 111.0, 120.9, 123.0, 124.1, 129.0, 137.7, 146.2, 151.3, 154.6, 166.4; IR (KBr) 3131, 2973, 2937, 2917, 1632, 1444 cm⁻¹; ESI-MS *m/z*: calcd for C₁₄H₁₂N₃OS [M+H]⁺, 270.0701; found, 270.0676. Anal. Calcd for C₁₄H₁₁N₃OS: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.28; H, 4.42; N, 15.53%.

4-(2-Ethylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)-5-methyl-3-phenylisoxazole (11) Colorless needle (EtOH), mp 132.0–133.5 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.43 (t, *J* = 7.6 Hz, 3H), 2.66 (s, 3H), 3.02 (q, *J* = 7.6 Hz, 2H), 7.35 (s, 1H), 7.38–7.47 (m, 3H), 7.57–7.65 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 12.3, 13.0, 25.7, 109.6, 111.8, 128.6, 128.7, 129.4, 129.5, 135.8, 144.9, 161.3, 166.0, 168.0; IR (KBr) 3115, 2972, 1641, 1528, 1468, 1241, 1185, 1056 cm⁻¹; ESI-MS *m/z*: calcd for C₁₆H₁₄N₄NaOS [M+Na]⁺, 333.0786; found, 333.0785. Anal. Calcd for C₁₆H₁₄N₄OS: C, 61.92; H, 4.55; N, 18.05. Found: C, 61.88; H, 4.63; N, 17.99%.

ACKNOWLEDGEMENTS

This work was supported in part by a Grant for the Regional Innovation Cluster Program (Global Type) promoted by MEXT.

REFERENCES AND NOTES

1. B. A. Bhongade, S. Talath, R. A. Gadad, and A. K. Gadad, *J. Saudi Chem. Soc.*, 2014, in press.
2. G. Tegginamath, R. R. Kamble, T. Taj, P. P. Kattimani, and G. Y. Meti, *Med. Chem. Res.*, 2013, **22**, 4367; M. N. Noolvi, H. M. Patel, S. Kamboj, A. Kaur, and V. Mann, *Eur. J. Med. Chem.*, 2012, **56**, 56; M. N. Noolvi, H. M. Patel, N. Singh, A. K. Gadad, S. S. Cameotra, and A. Badiger, *Eur. J. Med. Chem.*, 2011, **46**, 4411; S. S. Karki, K. Panjamurthy, S. Kumar, M. Nambiar, S. A. Ramareddy, K. K. Chiruvella, and S. C. Raghavan, *Eur. J. Med. Chem.*, 2011, **46**, 2109; N. Terzioglu and A. Gürsoy, *Eur. J. Med. Chem.*, 2003, **38**, 781.
3. T. M. Gireesh, R. R. Kamble, and T. Taj, *Pharm. Chem. J.*, 2011, **45**, 313.
4. K. F. M. Atta, O. O. M. Farahat, A. Z. A. Ahmed, and M. G. Marei, *Molecules*, 2011, **16**, 5496; A. K. Gadad, C. S. Mahajanshetti, S. Nimbalkar, and A. Raichurkar, *Eur. J. Med. Chem.*, 2000, **35**, 853.
5. S. D. Joshi, K. Manish, and A. Badiger, *Med. Chem. Res.*, 2013, **22**, 869.
6. B. Chandrakantha, A. M. Isloor, P. Shetty, H. K. Fun, and G. Hegde, *Eur. J. Med. Chem.*, 2014, **71**, 316.
7. V. K. Bhovi and Y. D. Bodke, *Curr. Chem. Biol.*, 2010, **4**, 145.
8. S. G. Alegaon, K. R. Alagawadi, P. V. Sonkusare, S. M. Chaudhary, D. H. Dadwe, and A. S. Shah, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1917; G. Kolavi, V. Hegde, I. A. Khazi, and P. Gadad, *Bioorg. Med. Chem.*, 2006, **14**, 3069; A. K. Gadad, M. N. Noolvi, and R. V. Karpoornath, *Bioorg. Med. Chem.*, 2004, **12**, 5651.
9. C. S. Andotra, T. C. Langer, and A. Kotha, *J. Indian Chem. Soc.*, 1997, **74**, 125.
10. P. Kumar, *Chin. J. Chem.*, 2010, **28**, 250.
11. S. G. Alegaon and K. R. Alagawadi, *Eur. J. Chem.*, 2011, **2**, 94; F. A. Ashour, N. S. Habib, M. El

- Taibbi, S. El Dine, and A. S. El Dine, *Il Farmaco*, 1990, **45**, 1341.
12. I. A. Khazi, C. S. Mahajanshetti, A. K. Gadad, A. D. Tarnalli, and C. M. Sultanpur, *Arzneim. Forsch.*, 1996, **46**, 949.
 13. H. M. Patel, M. N. Noolvi, A. Goyal, and B. S. Thippeswamy, *Eur. J. Med. Chem.*, 2013, **65**, 119.
 14. V. B. Jadhav, M. V. Kulkarni, V. P. Rasal, S. S. Biradar, and M. D. Vinay, *Eur. J. Med. Chem.*, 2008, **43**, 1721.
 15. A. Andreani, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, W. A. Simon, and J. Senn-Bilfinger, *Arzneim. Forsch.*, 2000, **50**, 550.
 16. A. H. Salehi, S. J. Morris, W.-C. Ho, K. M. Dickson, G. Doucet, S. Milutinovic, J. Durkin, J. W. Gillard, and P. A. Barker, *Chem. Biol.*, 2006, **13**, 213.
 17. A. Marin, N. Valls, F. J. Berenguer, M. T. Alonso, A. Ramon Martínez, M. Mercedes Martínez, and J. Elguero, *Il Farmaco*, 1992, **47**, 63.
 18. A. Andreani, M. Rambaldi, A. Locatelli, S. Malandrino, and G. Pifferi, *Arzneim. Forsch.*, 1994, **44**, 618.
 19. V. J. Ram and N. Haque, *Indian J. Chem., Sec B*, 1996, **35B**, 238.
 20. A. Andreani, M. Rambaldi, A. Locatelli, R. Bossa, G. Salvatore, and I. Galatulas, *Eur. J. Med. Chem.*, 1994, **29**, 339.
 21. K. Ohta, S. Itoh, Y. Kandou, H. Yoshikawa, and Y. Ishida, *J. Pesticide Sci.*, 1994, **19**, 137.
 22. T. Zarganes-Tzitzikas, C. G. Neochoritis, J. Stephanidou-Stephanatou, C. A. Tsoleridis, G. Buth, and G. E. Kostakis, *Tetrahedron*, 2013, **69**, 5008.
 23. T. Matsukawa and S. Ban, *Yakugaku Zasshi*, 1952, **72**, 610.
 24. M. Kidwai, D. Bhatnagar, and R. Chauhan, *J. Heterocycl. Chem.*, 2013, **50**, E234; S. Dhepe, S. Kumar, R. Vinayakumar, S. A. Ramareddy, and S. S. Karki, *Med. Chem. Res.*, 2012, **21**, 1550; K. Tiwari, P. K. Verma, S. B. Singh, and J. Singh, *Synth. Commun.*, 2012, **42**, 3021; C. Copin, N. Henry, F. Buron, and S. Routier, *Eur. J. Org. Chem.*, 2012, 3079; I. A. M. Khazi, A. K. Gadad, R. S. Lamani, and B. A. Bhongade, *Tetrahedron*, 2011, **67**, 3289.
 25. X. Wang, M. Wang, Z. Quan, and Z. Li, *Synth. Commun.*, 2005, **35**, 2881; X.-C. Wang, M.-G. Wang, Z. Yang, Z.-J. Quan, F. Wang, and Z. Li, *J. Chem. Res.*, 2005, **11**, 744.
 26. Crystal data for **41**: C₁₆H₁₇BrN₄O₂S, *M* = 409.30, monoclinic, *P*2₁/a (No. 14), *a* = 12.015(1) Å, *b* = 10.039(1) Å, *c* = 16.092(2) Å, β = 93.953(3) °, *V* = 1936.5(4) Å³, *Z* = 4, *D*_{calc} = 1.404 g/cm³, μ(Mo-Kα) = 22.51 cm⁻¹. Deposition number CCDC-980273 for compound **41** contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
 27. Crystal data for **11**: C₁₆H₁₄N₄OS, *M* = 310.37, triclinic, *P*-1 (No. 2), *a* = 5.6466(3) Å, *b* = 11.1503 (6)

\AA , $c = 12.9232(9) \text{\AA}$, $\alpha = 66.584(3)^\circ$, $\beta = 82.763(3)^\circ$, $\gamma = 89.608(2)^\circ$, $V = 739.87(8) \text{\AA}^3$, $Z = 2$, $D_{\text{calc}} = 1.393 \text{ g/cm}^3$, $\mu(\text{Mo-K}\alpha) = 2.26 \text{ cm}^{-1}$. Deposition number CCDC-980272 for compound **11** contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

28. M. Kidwai and S. Rastogi, *Indian J. Chem., Sec B*, 2006, **45B**, 2321; M. Kidwai and S. Rastogi, *Lett. Org. Chem.*, 2006, **3**, 149.
29. S. Ban, *Yakugaku Zasshi*, 1954, **74**, 1044.
30. R. Rani and J. K. Makrandi, *Indian J. Heterocycl. Chem.*, 2008, **18**, 121.