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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

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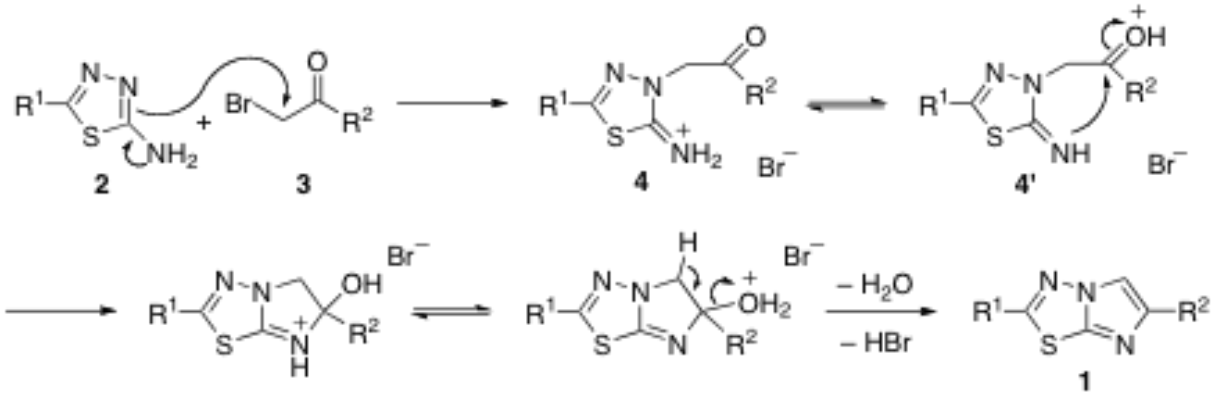
Abstract – The synthesis of 1,3,4-thiadiazol-2(3*H*)-iminium bromides, which are intermediates in the most commonly used synthetic approach to imidazo[2,1-*b*][1,3,4]thiadiazoles, and a single crystal X-ray diffraction study of one of these iminium bromides are described. Cyclization of the resulting 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] anticonvulsant[12] and antihyperlipidemic[13] activities. In addition, anti-inflammatory,[10,14] antisecretory,[15] antiapoptotic,[16] anthelmintic,[17] diuretic,[18] leishmanicidal,[19] cardiotonic,[20] and herbicidal[21] effects have also been reported. Thus, the imidazo[2,1-*b*][1,3,4]thiadiazoles are thought to have tremendous potential in medicinal chemistry.

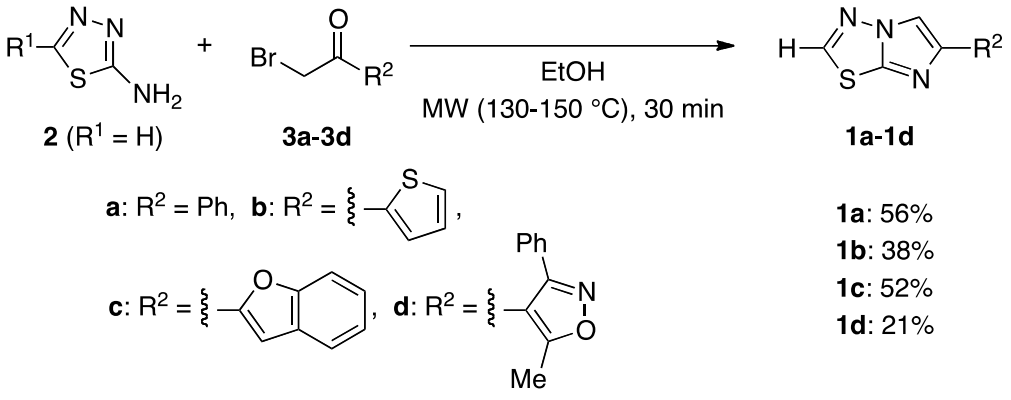
Recently, a novel method for synthesizing imidazo[2,1-*b*][1,3,4]thiadiazoles by the reaction of 4,5-disubstituted-*N*-arylaminoimidazole-2-thiones with isocyanides in the presence of azodicarboxylates has been reported.[22] However, the most commonly used method for the preparation of imidazo[2,1-*b*][1,3,4]thiadiazole **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**

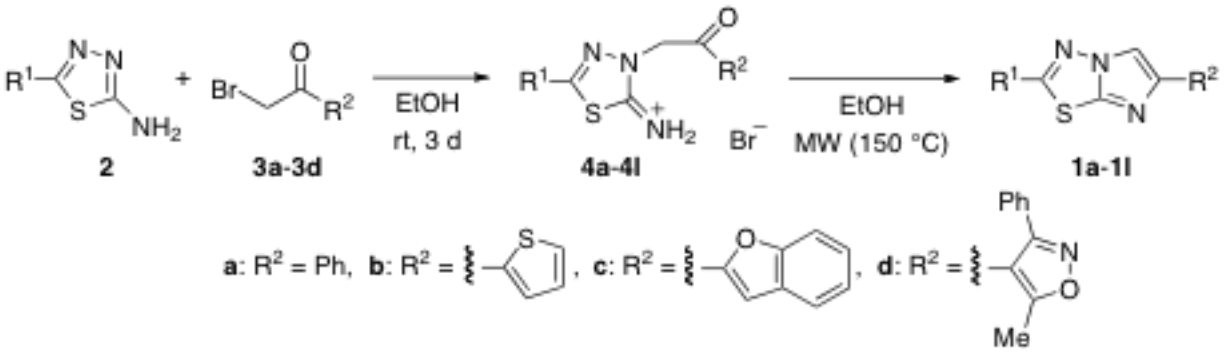
First, we synthesized imidazo[2,1-*b*][1,3,4]thiadiazoles **1a-1d** utilizing an ordinary one-pot synthetic method. Thus, a mixture of 2-amino-1,3,4-thadiazole **2** (R^1 = H) and 1mol eq. of α-haloketone **3** [R^2 = Ph, 2-thiophenyl, 2-benzofuranyl, and 4-(5-methyl-3-phenylisoxazolyl)] underwent a known reaction under microwave irradiation[25] with a single-mode microwave reactor (Initiator^{TM} 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 = H, Me, and Et) and 1mol eq. of **3** [R^2 = 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.

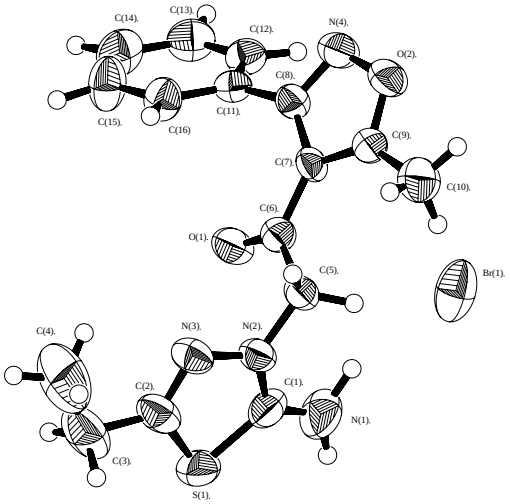


Figure 1. ORTEP drawing of 1,3,4-thiadiazol-2(3*H*)-iminium bromide **4l**

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 (Initiator^{TM} 60; Biotage AB). The cyclization of 1,3,4-thiadiazol-2(3*H*)-iminium bromides **4a-4l** under microwave irradiation at 150 °C in ethanol consequently afforded the desired cyclized compounds **1a-1l** in excellent yields (Scheme 3, Table 2). The structures of **1a-1l** were determined by spectroscopic methods. In addition, the structure of **1l** 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-1l**

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 (**1l**)

[a] Isolated yields.

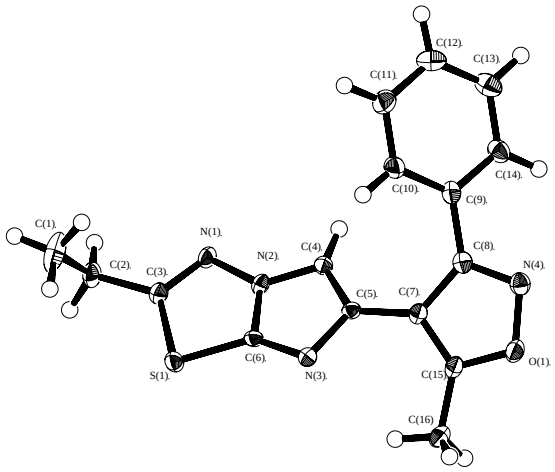


Figure 2. ORTEP drawing of imidazo[2,1-*b*][1,3,4]thiadiazole **1l**

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. ^{1}H 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 (Initiator^{TM} 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 F_{254}). 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** (R^1 = H) (129 mg, 1 mmol) and **3d** (280 mg, 1mmol) 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(3*H*)-iminium Bromide (4a)[23] Colorless solid; ^{1}H NMR (500 MHz, 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, 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 $C_{10}H_{10}N_3OS$ $[M–Br]^+$, 220.0545; found, 220.0535. Anal. Calcd for $C_{10}H_{10}BrN_3OS$: 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(3*H*)-iminium Bromide (4b) Yellow plate (MeOH); ^{1}H NMR (500 MHz, 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, 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 $C_8H_8N_3OS_2$ $[M–Br]^+$, 226.0109; found, 226.0093. Anal. Calcd for $C_8H_8BrN_3OS_2$: 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(3*H*)-iminium Bromide (4c) Pale red needle (MeOH—THF); ^{1}H NMR (500 MHz, 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, 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 $C_{12}H_{10}N_3O_2S$ $[M–Br]^+$, 260.0494; found, 260.0516. Anal. Calcd for $C_{12}H_{10}BrN_3O_2S$: 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(3*H*)-iminium Bromide (4d) Colorless solid; ^{1}H NMR (500 MHz, 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, 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 $C_{14}H_{13}N_4O_2S$ $[M–Br]^+$, 301.0759; found, 301.0764.

5-Methyl-3-(2-oxo-2-phenylethyl)-1,3,4-thiadiazol-2(3*H*)-iminium Bromide (4e)[23] Colorless solid; ^{1}H NMR (500 MHz, 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, 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 $C_{11}H_{12}N_3OS$ $[M–Br]^+$, 234.0701; found, 234.0683. Anal. Calcd for $C_{11}H_{12}BrN_3OS$: 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(3*H*)-iminium Bromide (4f) Brown solid; ^{1}H NMR (500 MHz, 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, 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 $C_9H_{10}N_3OS_2$ $[M–Br]^+$, 240.0265; found, 240.0243. Anal. Calcd for $C_9H_{10}BrN_3OS_2$: 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(3*H*)-iminium Bromide (4g) Colorless solid; ^{1}H NMR (500 MHz, 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, 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 $C_{13}H_{12}N_3O_2S$ $[M–Br]^+$, 274.0650; found, 274.0655. Anal. Calcd for $C_{13}H_{12}BrN_3O_2S$: 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(3*H*)-iminium Bromide (4h) Colorless needle (MeOH); ^{1}H 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 $C_{15}H_{15}N_4O_2S$ $[M–Br]^+$, 315.0916; found, 315.0917. Anal. Calcd for $C_{15}H_{15}BrN_4O_2S$: 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(3*H*)-iminium Bromide (4i)[23] Colorless needle (MeOH); ^{1}H NMR (500 MHz, 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, 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 $C_{12}H_{13}N_3NaOS$ $[M–HBr+Na]^+$, 270.0677; found, 270.0665. Anal. Calcd for $C_{12}H_{14}BrN_3OS$: 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(3*H*)-iminium Bromide (4j) Colorless solid; ^{1}H 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 $C_{10}H_{11}N_3NaOS_2$ [M–HBr+Na]$^+$, 276.0241; found, 276.0267. Anal. Calcd for $C_{10}H_{12}BrN_3OS_2$: 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(3*H*)-iminium Bromide (4k) Colorless solid; ^{1}H 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 $C_{14}H_{14}N_3O_2S$ [M–Br]$^+$, 288.0807; found, 288.0821. Anal. Calcd for $C_{14}H_{14}BrN_3O_2S$: 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(3*H*)-iminium Bromide (4l) Colorless column (MeOH); ^{1}H 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 $C_{16}H_{17}N_4O_2S$ [M–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); ^{1}H 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 $C_{10}H_8N_3S$

$[M+H]^+$, 202.0439; found, 202.0443. Anal. Calcd for $C_{10}H_7N_3S$: 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 ($CHCl_3$—*n*-hexane), mp 124.0–125.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_8H_6N_3S_2$ $[M+H]^+$, 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; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{12}H_7N_3NaOS$ $[M+Na]^+$, 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; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{10}N_4NaOS$ $[M+Na]^+$, 305.0473; found, 305.0455. Anal. Calcd for $C_{14}H_{10}N_4OS$: 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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{11}H_9N_3NaS$ $[M+Na]^+$, 238.0415; found, 238.0408. Anal. Calcd for $C_{11}H_9N_3S$: 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; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_9H_8N_3S_2$ $[M+H]^+$, 222.0160; found, 222.0170. Anal. Calcd for $C_9H_7N_3S_2$: 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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{13}H_9N_3NaOS$ $[M+Na]^+$, 278.0364; found, 278.0354. Anal. Calcd for $C_{13}H_9N_3OS$: 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; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{15}H_{12}N_4NaOS$ $[M+Na]^+$, 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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{12}H_{12}N_3S$ $[M+H]^+$, 230.0752; found, 230.0752. Anal. Calcd for $C_{12}H_{11}N_3S$: 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; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{10}H_{10}N_3S_2$ $[M+H]^+$, 236.0316; found, 236.0302. Anal. Calcd for $C_{10}H_9N_3S_2$: 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; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{12}N_3OS$ $[M+H]^+$, 270.0701;

found, 270.0676. Anal. Calcd for $C_{14}H_{11}N_3OS$: 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 (1l) Colorless needle (EtOH), mp 132.0–133.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{16}H_{14}N_4NaOS$ $[M+Na]^+$, 333.0786; found, 333.0785. Anal. Calcd for $C_{16}H_{14}N_4OS$: C, 61.92; H, 4.55; N, 18.05. Found: C, 61.88; H, 4.63; N, 17.99%.

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26. Crystal data for **4l**: $C_{16}H_{17}BrN_4O_2S$, M = 409.30, monoclinic, $P2_1/a$ (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) Å^3, Z = 4, D_{calc} = 1.404 g/cm^3, μ(Mo-Kα) = 22.51 cm^{-1}. Deposition number CCDC-980273 for compound **4l** 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 **1l**: $C_{16}H_{14}N_4OS$, M = 310.37, triclinic, P-1 (No. 2), a = 5.6466(3) Å, b = 11.1503 (6) Å, c = 12.9232(9) Å, α = 66.584(3) °, β = 82.763(3) °, γ = 89.608(2) °, V = 739.87(8) $Å^3$, Z = 2, D_{calc} = 1.393 g/cm^3, μ(Mo-Kα) = 2.26 cm^{-1}. Deposition number CCDC-980272 for compound **1l** 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.
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