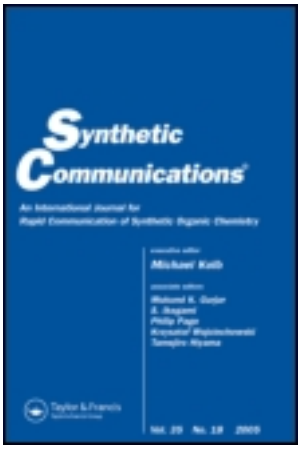

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Unexpected Microwave Reaction of 1,3-Disubstituted Imidazolium Salts: A Novel Synthesis of 1,3-Disubstituted Imidazole-2-thiones

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Unexpected Microwave Reaction of 1,3-Disubstituted Imidazolium Salts: A Novel Synthesis of 1,3-Disubstituted Imidazole-2-thiones

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Abstract: Microwave-promoted reaction of 1,3-disubstituted imidazolium salts with potassium thioacetate or potassium thiocyanate under solvent-free conditions provided a rapid and efficient synthesis of 1,3-disubstituted imidazole-2-thiones.

Keywords: microwave, imidazole-2-thiones, potassium thioacetate, potassium thiocyanate

Imidazole-2-thiones are important organic compounds that have attracted considerable attention because of their pharmacological activities. Some imidazole-2-thione derivatives, such as 1-methylimidazole-2-thione (Methimazole®), have been clinically used for the treatment of several diseases.[1–3] Imidazole-2-thione C-nucleosides are synthetic precursors of azidonucleosides and fluronucleosides, which possess anti-AIDS activity.[4] Imidazole-2-thiones have been used as rubber antioxidants[5] and as accelerators of rubber vulcanization in industry.[6] 1,3-Disubstituted imidazole-2-thiones are a class of versatile catalysts.[7,8] Furthermore, imidazole-2-thiones are light-sensitive photographic[9] and high-speed photothermographic materials.[10] Additionally, 1-propenyl-3-methylimidazole-2-thione is very useful in the manufacture of printed circuit board.[11] Traditionally, imidazole-2-thiones are prepared by reaction of an imidazolium ion with

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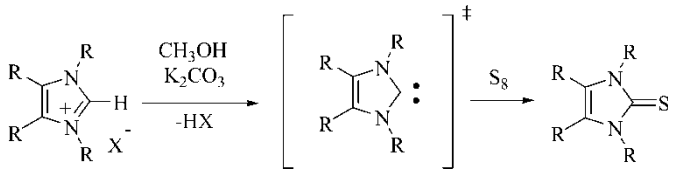
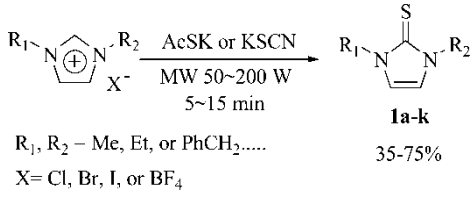


Scheme 1.

sulfur in the presence of methanolic potassium carbonate (Scheme 1),[12] or with sulfur dioxide, sulfines, or *N*-sulfinylamines.[13] In the reaction of imidazolium ion with sulfur, imidazol-2-ylidenes (carbenes) formed by deprotonation of the imidazolium cations were presumed to be intermediates. The synthesis is remarkably insensitive to varied conditions that allow different substituents to be accommodated on the imidazole ring. The reaction can even be run under dry air, but moisture is not well tolerated.[14] As part of our interest in microwave-promoted organic transformations,[15] herein we report a new procedure for the synthesis of 1,3-disubstituted imidazole-2-thiones under microwave irradiation and solvent-free conditions.

In our initial experiments, we found unexpected that when a mixture of 1,3-disubstituted imidazolium salt and potassium thioacetate was heated under microwave irradiation (50–200 W) for 5–15 min, 1,3-disubstituted imidazole-2-thiones **1** could be obtained in moderate yields (Scheme 2 method A). A variety of 1,3-disubstituted imidazolium salts were examined, and the results are summarized in Table 1 Interestingly, when we replaced potassium thioacetate with potassium thiocyanate (Scheme 2) the same products were obtained in improved yields under similar conditions (Table 1 method B). It is noteworthy that the reaction did not work when conventional heating was used.

As shown in Table 1, when irradiated at 50 W for 5 min, 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (bmim·BF_4) was transformed into **1a** in a comparatively low yield (method A: 45%, method B: 52%) (Table 1 entry 1). Both increasing the irradiation power (up to 100 W) and prolonging the reaction time (up to 10 min) could improve the yields (Table 1, entries 2 and 3). However, further increasing the irradiation power (up to 200 W) led to lower yields (Table 1, method A: entries 3 and 4; method B: entry 4).



Scheme 2.

Table 1. Microwave-assisted synthesis of 1,3-disubstituted imidazole-2-thiones[a]

Entry	R_1	R_2	X	Time (min)		Power (w)		Products	Isolated yield (%)	
				A	B	A	B		A	B
1	Me	Bu	BF_4	5	5	50	50	**1a**	45	52
2	Me	Bu	BF_4	10	10	100	100	**1a**	60	62
3	Me	Bu	BF_4	10	10	150	150	**1a**	48	70
4	Me	Bu	BF_4	15	15	200	200	**1a**	35	60
5	Me	Bu	Br	10	10	100	150	**1a**	60	68
6	Me	Bu	Cl	10	10	100	150	**1a**	58	66
7	Me	Me	I	8	10	100	150	**1b**	52	65
8	Me	Et	Br	10	10	100	150	**1c**	55	68
9	Et	Bu	Cl	10	10	100	150	**1d**	63	69
10	Et	$CH_2CH(CH_3)_2$	Cl	10	10	100	150	**1e**	65	70
11	Me	$CH_3(CH_2)_{11}$	Br	10	10	100	150	**1f**	70	70
12	Me	$PhCH_2$	Br	10	10	150	200	**1g**	65	68
13	Me	CH_2CO_2Et	Br	10	10	100	150	**1h**	65	65
14	Me	$CH_2CH{=}CH_2$	Br	8	8	100	150	**1i**	58	62
15	$PhCH_2$	$PhCH_2$	Br	10	10	150	200	**1j**	70	75
16	Et	$PhCH_2$	Br	10	10	100	150	**1k**	68	75

[a]Method A: methylimidazolium (5 mmol), potassium thioacetate (1.2 equiv), 50–200 W power, 5–15 min.
Method B: methylimidazolium (5 mmol), potassium thiocyanate (1.2 equiv), 50–200 W power, 5–15 min.

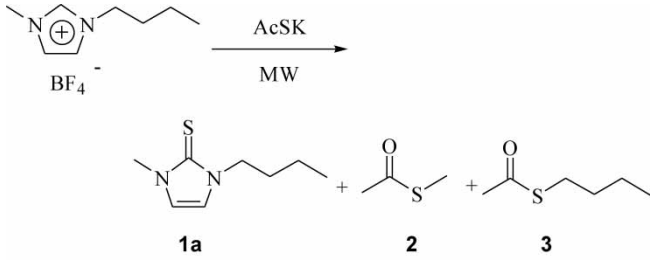
We investigated the by-products for the synthesis of 1-*n*-butyl-3-methylimidazole-2-thione (**1a**). *S*-Methyl ethanethioic acid ester (**2**) and *S*-butyl ethanethioic acid ester (**3**) were detected by gas chromatography-mass spectra (GC-MS). These products presumably resulted from the nucleophilic attack of potassium thioacetate on the methyl and butyl groups of the imidazolium cation (Scheme 3). For this reason, it can be presumed that the bulky group substituted imidazolium salts (Table 1, entries 11 and 16) should give comparatively higher yields than the small group substituted imidazolium salts (Table 1, entries 7 and 8). These observations were also accordance with Gleen's report that 1,3-dialkylimidazolium cation decomposes in the presence of nucleophiles (thiophenol, sodium thiophenolate, etc.) under microwave-heating conditions.[16]

In the reaction of 1-hydroylethyl-3-methyl imidazolium chloride (**4**) with potassium thioacetate (1.2 equiv), besides the expected product **5**[8,9] (24% yield), acetyl substituted imidazole-2-thione (**6**) was also isolated in 32% yield. When 2.5 equiv of potassium thioacetate was used, compound **6** was obtained in 63% yield as a single product (Scheme 4).

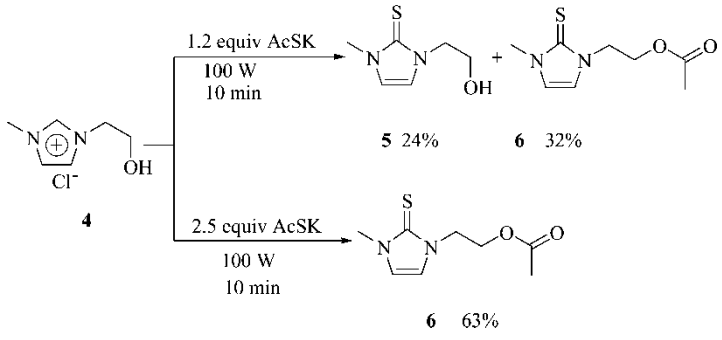
The method was also applied for synthesis of the bridged imidazole-2-thione **8**, a ligand that could form complexes with mercury, palladium, and copper salts[17] from the corresponding imidazolium salt **7** as show in Scheme 5.

In a comparative experiment, the present procedure gave compound **1 h** in 65% yield, whereas the traditional method[13] resulted in a imidazole-2-thione **9** with ester exchange in poor yield (Scheme 6). It is noteworthy that the reaction could be carried out in the presence of a small amount of a water using our procedure.

In summary, we have developed a practical synthesis of 1,3-disubstituted imidazole-2-thiones via a microwave-promoted reaction of imidazolium salts with potassium thioacetate or potassium thiocyanate under solvent-free conditions. Compared with the traditional methods, the present protocol is rapid, facile, and efficient. The reaction could be carried out in the presence of a small amount of water. The mechanisms of these transformations are under investigation and will be reported due course.



Scheme 3.



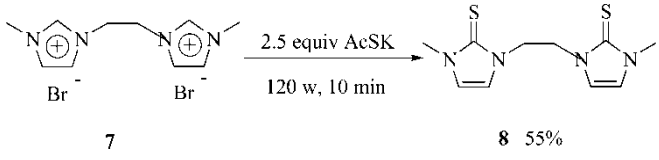
Scheme 4.

EXPERIMENTAL

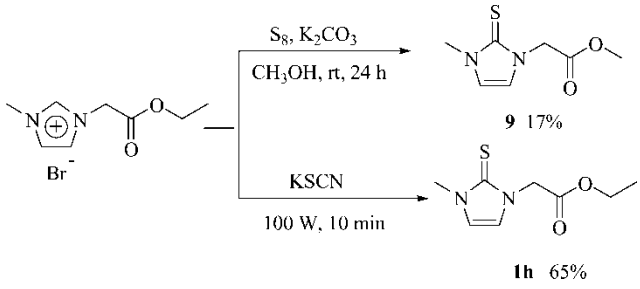
All chemicals were reagent grade and used as purchased. ^{1}H NMR spectra were recorded in deuterated solvent on Bruker Avance-500 spectrometer operating at 500 MHz or on Bruker Avance-300 spectrometer operating at 300 MHz. ^{13}C NMR spectra were recorded at 125 MHz. Infrared spectra were recorded on a Nicolet 470 Nexus FT-IR spectrometer and measured as thin film or in KBr. ESI-MS spectra were recorded on a Bruker Daltonics Esquire 3000 plus instrument. Melting points were measured on WRS-1B digital melting-point apparatus. Capillary gas chromatography was performed on a Hewlett-Packard HP 6890 gas chromatograph/mass spectra instrument (GC/MS).

General Procedure for Synthesis of 1,3-Disubstituted Imidazole-2-thiones

1-*n*-Butyl-3-methyl-imidazolium tetrafluoroborate (5 mmol) and potassium thioacetate or potassium thiocyanate (1.2 equiv) were mixed thoroughly and then irradiated at 100 W for 10 min. (In the case of the reaction using potassium thiocyanate, direct contact with the possible cyanide by-products, such as hydrogen cyanide (HCN) and cyanopotassium (KCN), should be avoided, although they have not been confirmed.) The mixture was cooled to room temperature, diluted with ethyl ether (25 ml), washed with water,



Scheme 5.



Scheme 6.

and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a crude product, which was purified by column chromatography on silica gel using EtOAc/hexane (1:4) to give pure 1-*n*-butyl-3-methylimidazole-2-thione (**1a**).

Data

1-*n*-Butyl-3-methylimidazole-2-thione (**1a**): Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.71$ (*d*, 1H, $J = 2.3$ Hz), 6.70 (*d*, 1H, $J = 2.3$ Hz), 4.03 (*t*, 2H, $J = 7.4$ Hz), 3.61 (*s*, 3H), 1.74–1.77 (*m*, 2H), 1.35–1.40 (*m*, 2H), 0.96 (*t*, 3H, $J = 7.4$ Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.4$, 117.7, 116.6, 47.8, 35.1, 31.0, 19.8, 13.7 ppm; FT-IR (neat): 3108, 3094, 2976, 2936, 1568, 1462, 1415, 1330, 1263, 1223, 1168 cm^{-1}; MS (ESI): m/z 171 ($[M+H]^+$).

1,3-Dimethylimidazole-2-thione (**1b**): White solid; mp 182–183.8°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.71$ (*s*, 2H), 3.57 (*s*, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.1$, 117.7, 40.7 ppm; FT-IR (KBr): 3105, 3098, 2980, 2933, 1569, 1458, 1420, 1330, 1271, 1219, 1158 cm^{-1}; MS (ESI): m/z 129 ($[M + H]^+$).

1-Ethyl-3-methylimidazole-2-thione (**1c**): Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.70$ (*d*, 1H, $J = 2.2$ Hz), 6.69 (*d*, 1H, $J = 2.2$ Hz), 4.08 (*q* 2H, $J = 7.1$ Hz), 3.61 (*s*, 3H), 1.37 (*t*, 2H, $J = 7.2$ Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.1$, 117.9, 116.0, 43.1, 35.2, 14.4 ppm; FT-IR (neat): 3098, 3078, 2976, 2936, 1568, 1465, 1425, 1327, 1268, 1223, 1161 cm^{-1}; MS (ESI): m/z 143 ($[M+H]^+$).

1-*n*-Butyl-3-ethylimidazole-2-thione (**1d**): Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.71$ (*d*, 1H, $J = 2.3$ Hz), 6.70 (*d*, 1H, $J = 2.3$ Hz), 4.10 (*q*, 2H, $J = 7.2$ Hz), 4.01 (*t*, 2H, $J = 7.4$ Hz), 1.74–1.77 (*m*, 2H), 1.38–1.42 (*m*, 2H), 1.38 (*t*, 3H, $J = 7.2$ Hz), 0.95 (*t*, 3H, $J = 7.3$ Hz) ppm; ^{13}C NMR

(125 MHz, $CDCl_3$): $\delta = 162.3$, 117.9, 116.6, 46.8, 35.1, 31.1, 19.8, 14.4, 13.7 ppm; FT-IR (neat): 3106, 3082, 2976, 2944, 1570, 1467, 1415, 1335, 1263, 1224, 1173 cm^{-1}; MS (ESI): m/z 185 ($[M+H]^+$); anal. calcd. for $C_9H_{16}N_2S$: C, 58.65; H, 8.75; N, 15.20. Found: C, 58.75; H, 8.79; N, 15.08.

1-*iso*-Butyl-3-ethylimidazole-2-thione (**1e**): Brown oil; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.71$ (*d*, 1H, $J = 2.1$ Hz), 6.67 (*d*, 1H, $J = 2.1$ Hz), 4.11 (*q*, 2 H, $J = 5.4$ Hz), 3.86 (*d*, 2H, $J = 7.4$ Hz), 2.20–2.26 (*m*, 1H), 1.37 (*t*, 3H, $J = 7.4$ Hz), 0.95 (*d*, 6H, $J = 6.7$ Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.8$, 117.8, 115.8, 55.3, 42.9, 29.9, 28.2, 20.1, 14.4 ppm; FT-IR (neat): 3103, 3094, 2966, 2940, 1568, 1463, 1414, 1337, 1263, 1223, 1170 cm^{-1}; MS (ESI): m/z 185 ($[M+H]^+$); anal. calcd. for $C_9H_{16}N_2S$: C, 58.65; H, 8.75; N, 15.20. Found: C, 58.73; H, 8.80; N, 15.10.

1-*n*-Dodecyl-3-methylimidazole-2-thione (**1f**): Brown oil; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.72$ (*d*, 1H, $J = 2.3$ Hz), 6.70 (*d*, 1H, $J = 2.3$ Hz), 4.03 (*t*, 2H, $J = 7.4$ Hz), 3.61 (*s*, 3H), 1.73–1.75 (*m*, 2H), 1.28–1.30 (*m*, 18H), 0.96 (*t*, 3 H, $J = 7.4$ Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.5$, 117.8, 116.6, 47.7, 35.4, 31.0, 28.5, 27.6, 27.2, 26.8, 26.5, 26.2, 25.8, 25.5, 19.8, 13.7 ppm; FT-IR (neat): 3105, 3088, 2965, 2935, 1572, 1470, 1425, 1338, 1255, 1223, 1172 cm^{-1}; MS (ESI): m/z 283 ($[M+H]^+$); anal. calcd. for $C_{16}H_{30}N_2S$: C, 68.03; H, 10.70; N, 9.92. Found: C, 68.25; H, 10.75; N, 9.87.

1-Benzyl-3-methylimidazole-2-thione (**1g**): Brown oil; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.29$–7.33 (*m*, 5H), 6.66 (*d*, 1H, $J = 2.2$ Hz), 6.56 (*d*, 1H, $J = 2.2$ Hz), 5.24 (*s*, 2H), 3.63 (*s*, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.4$, 129.0, 128.4, 128.2, 118.1, 116.4, 51.5, 35.4 ppm; FT-IR (neat): 3110, 3094, 2978, 2932, 1578, 1455, 1412, 1330, 1263, 1223, 1155 cm^{-1}; MS (ESI): m/z 205 ($[M+H]^+$).

1-Ethoxyacetyl-3-methylimidazole-2-thione (**1h**): Brown oil; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.78$ (*d*, 1H, $J = 2.2$ Hz), 6.74 (*d*, 1H, $J = 2.2$ Hz), 4.86 (*s*, 2H), 4.25 (*q*, 2H, $J = 7.1$ Hz), 3.61 (*s*, 3H) 1.30 (*t*, 3H, $J = 7.1$ Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.6$, 163.8, 118.0, 117.4, 62.0, 48.8, 35.4, 14.2 ppm; FT-IR (neat): 3126, 2987, 2936, 1732, 1570, 1466, 1425, 1403, 1389, 1250, 1224, 1147, 1029 cm^{-1}; MS (ESI): m/z 201 ($[M+H]^+$); anal. calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 47.95; H, 6.08; N, 13.86.

1-Propenyl-3-methylimidazole-2-thione (**1i**): Brown oil; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.71$ (*d*, 1H, $J = 2.3$ Hz), 6.70 (*d*, 1H, $J = 2.3$ Hz), 5.90–5.95 (*m*, 1H), 5.27 (*d*, 2H, $J = 1.0$ Hz), 4.68 (*d*, 2H, $J = 6.0$ Hz), 3.63 (*s*, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.6$, 132.1, 119.2, 117.9, 116.4, 50.4, 35.3 ppm; FT-IR (neat): 3159, 3110, 3091, 2979, 2925, 1644, 1568, 1459, 1398, 1344, 1242, 1210, 1157 cm^{-1}; MS (ESI): m/z 155 ($[M+H]^+$).

1,3-Dibenzylimidazole-2-thione (**1j**): Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.30–7.35$ (*m*, 10H), 6.53 (*s*, 2H), 5.29 (*s*, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 163.4$, 136.0, 129.1, 128.6, 128.4, 116.9, 51.6 ppm; FT-IR (neat): 3159, 3119, 3084, 3030, 2920, 1568, 1495, 1449, 1243, 1230 cm^{-1}; MS (ESI): m/z 281 ($[M+H]^+$); anal. calcd. for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99. Found: C, 72.95; H, 5.82; N, 9.93.

1-Benzyl-3-ethylimidazole-2-thione (**1k**): Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.29–7.33$ (*m*, 5H), 6.68 (*d*, 1H, $J = 2.3$ Hz), 6.57 (*d*, 1H, $J = 2.3$ Hz), 5.20 (*s*, 2H), 4.13 (*q*, 2H, $J = 7.4$ Hz), 1.38 (*t*, 3H, $J = 7.4$ Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.5$, 136.0, 128.9, 128.5, 128.1, 117.9, 116.2, 47.8, 35.1, 16.7 ppm; FT-IR (neat): 3110, 3083, 2971, 2925, 1568, 1465, 1419, 1322, 1262, 1217, 1162 cm^{-1}; MS (ESI): m/z 219 ($[M+H]^+$); anal. calcd. for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83. Found: C, 66.11; H, 6.52; N, 12.75.

1-Hydroxyethyl-3-methylimidazole-2-thione (**5**): Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.81$ (*d*, 1H, $J = 2.2$ Hz), 6.70 (*d*, 1H, $J = 2.2$ Hz), 4.24 (*t*, 2H, $J = 5.1$ Hz), 3.95 (*q*, 2H, $J = 5.1$ Hz), 3.61 (*s*, 3H), 2.76 (*t*, 1 H, $J = 5.1$ Hz, D_2O exchange) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.6$, 118.2, 117.9, 61.9, 50.6, 35.4 ppm; FT-IR (neat): 3380, 3159, 3120, 2960, 1570, 1460, 1422, 1235, 1161 cm^{-1}; MS (ESI): m/z 159 ($[M+H]^+$); anal. calcd. for $C_6H_{10}N_2OS$: C, 45.55; H, 6.37; N, 17.71. Found: C, 45.67; H, 6.45; N, 17.63.

1-Acetyloxyethyl-3-methylimidazole-2-thione (**6**): Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.73$ (*d*, 1H, $J = 1.9$ Hz), 6.69 (*d*, 1H, $J = 1.9$ Hz), 4.40 (*t*, 2H, $J = 5.1$ Hz), 4.31 (*t*, 2H, $J = 5.1$ Hz), 3.61 (*s*, 3H), 2.06 (*s*, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.7$, 162.6, 117.9, 117.5, 62.2, 47.0, 35.4, 21.0 ppm; FT-IR (neat): 3164, 3131, 2945, 1738, 1570, 1461, 1403, 1231, 1154 cm^{-1}; MS (ESI): m/z 201 ($[M+H]^+$); anal. calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 48.05; H, 6.12; N, 13.87.

1,1′-(1,2-Ethanediyl)bis(2,3-dihydro-3-methyl-1H-imidazole-2-thione) (**8**): White solid; mp 193.5–195.2°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.57$ (*d*, 2H, $J = 2.1$ Hz), 6.54 (*d*, 2H, $J = 2.1$ Hz), 4.44 (*s*, 4H), 3.56 (*s*, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.5$, 117.9, 45.6, 35.2 ppm; FT-IR (KBr): 3154, 3113, 2937, 1568, 1468, 1421, 1235, 1193, 675 cm^{-1}; MS (ESI): m/z 255 ($[M+H]^+$).

1-Methoxyacetyl-3-methylimidazole-2-thione (**9**): Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.82$ (*d*, 1H, $J = 2.2$ Hz), 6.80 (*d*, 1H, $J = 2.2$ Hz), 4.86 (*s*, 2H), 3.65 (*s*, 3H), 3.80 (*s*, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.9$, 163.5, 117.5, 117.2, 75.8, 55.6, 54.5 ppm; FT-IR (neat): 3120, 2987, 1735, 1572, 1464, 1427, 1405, 1388, 1250, 1224 cm^{-1}; MS (ESI):

m/z 187 ($[M+H]^+$); anal. calcd. for $C_7H_{10}N_2O_2S$: C, 45.15; H, 5.41; N, 15.04. Found: C, 45.23; H, 5.52; N, 14.98.

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