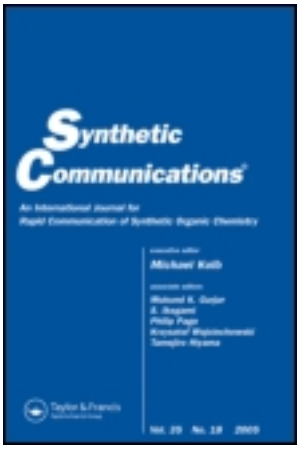

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One-Pot Preparation of 1-Substituted Imidazole-2-thione from Isothiocyanate and Amino Acetal

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ONE-POT PREPARATION OF 1-SUBSTITUTED IMIDAZOLE-2-THIONE FROM ISOTHIOCYANATE AND AMINO ACETAL

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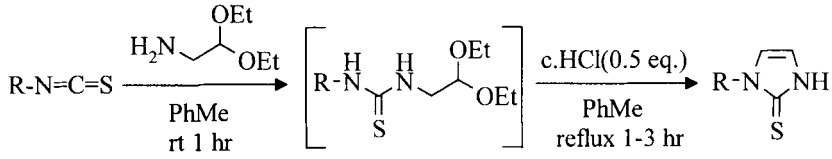
Abstract: Isothiocyanates were treated with amino acetal and conc. HCl (0.5 eq.) successively in one-pot to afford 1-substituted imidazole-2-thiones in good yields.

1-Substituted imidazole-2-thione is a valuable substrate for pharmaceutical synthesis.[1] Marckwald's method has long been known as a general



synthetic pathway to it,[2] in which isothiocyanate and amino acetal are heated in refluxing ethanol to form a thiourea derivative which is isolated and then heated in aqueous HCl to afford 1-substituted imidazole-2-thione. We modified this

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method into a one-pot fashion and found that the first thiourea forming step proceeded at room temperature in toluene and that the latter cyclization step took place with adding catalytic amount of conc. HCl immediately after the completion of the first step followed by heating without evaporating solvents or isolating the thiourea intermediate (Table).

Table

Entry	R-N=C=S	Solvent	Additive(eq.)	Time(hr)	Yield(%)[a]
1	4-Chlorophenyl	EtOH	c.HCl(1)	3	trace
2	4-Chlorophenyl	EtOH	AcOH(6)	3	-
3	4-Chlorophenyl	PhMe	AcOH(6)	3	trace
4	4-Chlorophenyl	PhMe	p-TSA(0.1)	3	mess
5	4-Chlorophenyl	PhMe	c.HCl(1)	3	84
6	4-Chlorophenyl	PhMe	c.HCl(0.5)	3	87(61[1b])
7	4-Chlorophenyl	PhMe	c.HCl(0.2)	3	75
8	3-Chlorophenyl	PhMe	c.HCl(0.5)	1	80(72[1b])
9	Phenyl	PhMe	c.HCl(0.5)	3	73(74[1a])
10	2-Methylphenyl	PhMe	c.HCl(0.5)	2	67(73[1a])
11	3-Methylphenyl	PhMe	c.HCl(0.5)	2	66(82[1a])
12	4-Methylphenyl	PhMe	c.HCl(0.5)	2	72(78[1a])
13	2-Methoxyphenyl	PhMe	c.HCl(0.5)	2	68(50[1b])
14	3-Trifluoromethylphenyl	PhMe	c.HCl(0.5)	3	90(92[1a])
15	3-Nitrophenyl	PhMe	c.HCl(0.5)	1	84(91[1a])
16	4-Nitrophenyl	PhMe	c.HCl(0.5)	3	96
17	4-Cyanophenyl	PhMe	c.HCl(0.5)	1	87(84[1a])
18	1-Naphthyl	PhMe	c.HCl(0.5)	3	82
19	4-Dimethylamino-1-naphthyl	PhMe	c.HCl(0.5)	2	92
20	Benzyl	PhMe	c.HCl(0.5)	2	53
21	Phenethyl	PhMe	c.HCl(0.5)	2	55
22	Cyclohexyl	PhMe	c.HCl(0.5)	2	43
23	Isobutyl	PhMe	c.HCl(0.5)	2	31

a) Yields in parenthesis are literature yields by the Marckwald's method.

First we tried to persuade the original method in one-pot (entry 1). Ethanol was employed as solvent. After forming the thiourea intermediate at room temperature, conc. HCl (1 eq.) was added and the mixture was refluxed for 3 hr to

form a trace amount of the product with the thiourea intermediate recovery. The reaction was apparently slow. In the case that acetic acid was used instead of HCl, the cyclization did not occur (entry 2). Next the solvent was changed to toluene (entries 3-7). The thiourea forming-step completed at room temperature in 1 hr as well as the case in ethanol. As for the second cyclization step, acetic acid gave a trace amount of the product with the thiourea recovery (entry 3), p-toluenesulfonic acid (0.1 eq.) resulted in a messy reaction (entry 4). On the other hand, conc. HCl gave fruitful results. One equivalent of conc. HCl gave 84 % of the product after refluxing 3 hr (entry 5). Furthermore, not only 1 eq. but also a catalytic amount of conc. HCl was good enough to carry out the reaction. 0.5 eq. and 0.2 eq of conc. HCl gave the product in 87 % and 75 % yields, respectively (entries 6 and 7). These reaction conditions, such as toluene/conc. HCl (0.5 eq.), were applied to other substrates. The results were summarized in Table (entries 8-23). The reaction worked on aromatic and alkyl isothiocyanates, while the latter gave lower yields. Aryl isothiocyanates gave the products in yields comparable to those obtained by the Marckwald's method.[1,2] As for the substituents on aryl group, Cl, CH_3, OCH_3, CF_3, NO_2, CN, and $N(CH_3)_2$ were tolerated during the reaction.

EXPERIMENTAL

Melting points were determined on a Yanaco MP-500D apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a HITACHI 270-30 spectrometer. NMR spectra were measured on a JEOL-EX-90, JNM-EX-400, or JNM-EX-500 spectrometers and the chemical shifts are expressed in ppm with TMS as an internal standard. MS spectra were recorded on a HITACHI M-80 or

JEOL-JMS-DX300 apparatus. Column chromatography was carried out using Merck Kieselgel 60(230-400 mesh). TLC was done on Merck DC-Fertigplatten Kieselgel 60 F_{254}.

Preparation of 1-substituted imidazole-2-thione (the general procedure): A mixture of isothiocyanate (5.0 mmol) and amino acetal (5.0 mmol) in toluene (10 ml) was stirred at room temperature for 1hr. To the reaction mixture, conc. HCl (37 wt. % in water, 2.5mmol) was added, followed by heating to reflux (bath temp.=110°) for the time indicated in Table. After evaporating the solvents, the residue was treated with water and 1N NaOH (pH was set to 8). The precipitates were collected by filtration, washed with water and hexane/ether, and dried *in vacuo* to give crude product which was recrystallized from an appropriate solvent shown below.

1-(4-Chlorophenyl)imidazole-2-thione, Colorless prisms (acetonitrile), mp. 225.5-226°C; lit. [1b] mp. 228-229°C; IR: 3154, 3112, 3028, 1578, 1500, 1476, 1419, 1320, 1284, 1269, 1251, 1089, 912, 837, 756, 741, and 573 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.83(1H, s), 6.85(1H, s), 7.48(2H, d, J=8.5 Hz), 7.57(2H, d, J=8.5 Hz), and 11.65(1H, s); MS (FAB): m/z 211($(M+H)^+$, base peak); *Anal.* Calcd. for $C_9H_7ClN_2S$: C, 51.31; H, 3.35; N, 13.30; S, 15.22; Cl, 16.83; Found: C, 51.21; H, 3.31; N, 13.30; S, 14.99; Cl, 16.91.

1-(3-Chlorophenyl)imidazole-2-thione, Colorless needles (acetonitrile), mp. 160.5-161.5°C; lit. [1b] mp. 159-160°C; IR: 3160, 1605, 1590, 1488, 1458, 1437, 1323, 1257, 1233, 1077, 774, 705, 687, and 669 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.10(1H, m), 7.37(1H, m), 7.49(1H, d, J=8.0 Hz), 7.54(1H, t, J=8.0 Hz), 7.64(1H, d, J=8.0 Hz), 7.84(1H, m), and 12.46(1H, s); MS: m/z 211($(M+H)^+$, base peak); *Anal.* Calcd. for $C_9H_7ClN_2S$: C, 51.31; H, 3.35; N, 13.30; S, 15.22; Cl, 16.83; Found: C, 51.19; H, 3.19; N, 13.38; S, 15.14; Cl, 16.89.

1-Phenylimidazole-2-thione, Colorless needles (benzene), mp. 182-183°C; lit. [2a] mp. 181°C; IR: 3094, 3022, 2920, 1602, 1578, 1506, 1482, 1419, 1332, 1311, 1275, 1254, 912, 801, 765, 714, 696, 678, and 573 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.83(2H, m), 7.3-7.7(5H, m), and 12.45(1H, s); MS: m/z 211(M^+), 175(base peak); *Anal.* Calcd. for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.89; S, 18.19; Found: C, 61.35; H, 4.66; N, 15.94; S, 18.02.

1-(2-Methylphenyl)imidazole-2-thione, Colorless needles (benzene-ethanol), mp. 247-248°C; lit. [1a] mp. 243-245°C; IR: 3100, 3016, 2926, 1578, 1506, 1479, 1416, 1323, 1290, 1251, 1146, 1101, 1089, 912, 795, 777, 720, 684, and 585 cm^{-1}; ^1H

NMR (DMSO-d_6): δ 2.09(3H, s), 7.0-7.4(6H, m), and 12.32(1H, s); MS: m/z 190(M^+), 157(base peak); *Anal.* Calcd. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; S, 16.85; Found: C, 63.09; H, 5.29; N, 14.64; S, 16.85.

1-(3-Methylphenyl)imidazole-2-thione, Colorless prisms (benzene), mp. 150-151°C; lit. [1a] mp. 147-149°C; IR: 3070, 3004, 2902, 1614, 1593, 1575, 1497, 1473, 1413, 1323, 1293, 1272, 1240, 912, 843, 816, 786, 726, 696, and 681 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.36(3H, s), 7.0-7.5(6H, m), and 12.34(1H, s); MS: m/z 190(M^+), 189(base peak); *Anal.* Calcd. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; S, 16.85; Found: C, 63.20; H, 5.43; N, 14.63; S, 16.83.

1-(4-Methylphenyl)imidazole-2-thione, Colorless prisms (benzene), mp. 208-208.5°C; lit. [2b] mp. 205°C; IR: 3070, 3004, 2902, 1614, 1593, 1575, 1497, 1473, 1413, 1323, 1293, 1272, 1240, 912, 843, 816, 786, 726, 696, and 681 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.35(3H, s), 7.05(1H, m), 7.23(1H, m), 7.29(2H, d, J=8.8 Hz), 7.50(2H, d, J=8.8 HZ), and 12.34(1H, s); MS: m/z 190(M^+), 189(base peak); *Anal.* Calcd. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; S, 16.85; Found: C, 63.09; H, 5.27; N, 14.71; S, 16.96.

1-(2-Methoxylphenyl)imidazole-2-thione, Colorless prisms (acetonitrile), mp. 227-228°C; lit. [1b] mp. 224-226°C; IR: 3148, 3106, 3022, 1605, 1575, 1509, 1473, 1446, 1422, 1320, 1278, 1245, 1198, 1152, 1101, 1020, 912, 771, 732, and 684 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.76(3H, s), 6.9-7.5(6H, m), and 12.22(1H, s); MS: m/z 206(M^+), 173(base peak); *Anal.* Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58; S, 15.55; Found: C, 58.23; H, 4.95; N, 13.59; S, 15.48.

1-(3-Trifluoromethylphenyl)imidazole-2-thione, Colorless plates (diethyl ether), mp. 160-161°C; lit. [1a] mp. 157-159°C; IR: 3118, 3028, 1488, 1461, 1338, 1323, 1311, 1278, 1269, 1179, 1134, 1092, 1071, 807, 780, 705, and 693 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.87(1H, d, J=2.3 Hz), 6.91(1H, d, J=2.3 Hz), 7.6-8.0(4H, m), and 12.33(1H, s); MS: m/z 244(M^+), 243(base peak); *Anal.* Calcd. for $C_{10}H_7F_3N_2S$: C, 49.18; H, 2.89; N, 11.47; F, 23.34; S, 13.13; Found: C, 49.06; H, 2.78; N, 11.44; F, 23.45; S, 13.13.

1-(3-Nitrophenyl)imidazole-2-thione, Yellow leaflets (benzene-ethanol), mp. 223-224°C; lit. [1a] mp. 223-224°C; IR: 3154, 3118, 3022, 1578, 1530, 1494, 1419, 1353, 1329, 1263, 1083, 792, 744, 729, and 678 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.16(1H, m), 7.50(1H, m), 7.81(1H, m), 8.16(1H, m), 8.27(1H, m), 8.70(1H, m), and 12.58(1H, s); MS(FAB): m/z 222($(M+H)^+$, base peak); *Anal.* Calcd. for $C_9H_7N_3O_2S$: C, 48.86; H, 3.19; N, 18.99; S, 14.49; Found: C, 48.96; H, 3.20; N, 18.85; S, 14.55.

1-(4-Nitrophenyl)imidazole-2-thione, Yellow prisms (acetonitrile), mp. 229-230.5°C; IR: 3136, 3040, 2938, 1602, 1584, 1527, 1506, 1479, 1413, 1344, 1317, 1260, 1146, 1113, 1080, 912, 855, 783, 750, 720, 687, 675, and 573 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.17(1H, d, J=2.5 Hz), 7.47(1H, d, J=2.5 Hz), 8.08(2H, d, J=9.2 Hz), 8.36(2H, d, J=9.2 Hz), and 12.58(1H, s); MS: m/z 221(M^+, base peak); *Anal.* Calcd. for $C_9H_7N_3O_2S$: C, 48.86; H, 3.19; N, 18.99; S, 14.49; Found: C, 48.66; H, 3.10; N, 19.07; S, 14.21.

1-(4-Cyanophenyl)imidazole-2-thione, Colorless prisms (methanol), mp. 270-271°C; lit. [1a] mp. 266-270°C; IR: 3106, 3034, 2932, 2230, 1611, 1593, 1575, 1515, 1482, 1413, 1326, 1293, 1263, 1185, 1146, 1089, 909, 846, 783, 720, 675, 585, and 573 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.15(1H, m), 7.43(1H, m), 7.99(4H, m), and 12.55(1H, s); MS(FAB): m/z 202($(M+H)^+$, base peak); *Anal.* Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; S, 15.93; Found: C, 59.57; H, 3.55; N, 20.86; S, 15.82.

1-(1-Naphthyl)imidazole-2-thione, Colorless needles (acetonitrile), mp. 252-252.5°C; lit. [2b] mp. 242°C; IR: 3094, 3022, 2926, 1602, 1578, 1515, 1488, 1422, 1314, 1290, 1254, 1092, 912, 804, 777, 717, and 681 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.84(1H, m), 6.90(1H, m), 7.5-7.7(5H, m), 7.9-8.1(2H, m) and 12.39(1H, s); MS(FAB): m/z 227($(M+H)^+$, base peak); *Anal.* Calcd. for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38; S, 14.17; Found: C, 69.00; H, 4.49; N, 12.42; S, 14.26.

1-(4-Dimethylamino-1-naphthyl)imidazole-2-thione, Colorless needles (methanol), mp. 276.5-277.5°C; IR: 3100, 3028, 2932, 1605, 1578, 1488, 1455, 1428, 1395, 1317, 1281, 1260, 1140, 1041, 855, 798, 771, 720, and 681 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.89(6H, s), 7.1-7.2(3H, m), 7.27(1H, d, J=8.0 Hz), 7.39(1H, d, J=8.0 Hz), 7.5-7.6(2H, m), 8.24(1H, d, J=8.4 Hz), and 12.42(1H, s); MS(FAB): m/z 270($(M+H)^+$, base peak); *Anal.* Calcd. for $C_{15}H_{15}N_3S$: C, 66.88; H, 5.61; N, 15.60; S, 11.90; Found: C, 66.71; H, 5.64; N, 15.50; S, 11.91.

1-Benzylimidazole-2-thione, Colorless prisms (benzene), mp. 149-150°C; lit. [3a] mp. 145-146°C; IR: 3100, 3028, 2932, 1576, 1479, 1443, 1413, 1362, 1278, 1248, 771, 726, 714, and 675 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.24(2H, s), 6.57(1H, d, J=2.3 Hz), 6.72(1H, d, J=2.3 Hz), 7.3-7.4(5H, m) and 11.74(1H, s); MS: m/z 190(M^+), 91(base peak); *Anal.* Calcd. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; S, 16.85; Found: C, 63.33; H, 5.33; N, 14.56; S, 16.71.

1-Phenethylimidazole-2-thione, Colorless needles (benzene), mp. 169.5-170.5°C; lit. [3b] mp. 166-167°C; IR: 3124, 3034, 2944, 1581, 1482, 1458, 1281, 1257, 1179,

732, 699, and 675 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.11(2H, t, J=7.3 Hz), 4.26(2H, t, J= 7.3 Hz), 6.36(1H, d, J=2.3 Hz), 6.61(1H, d, J=2.3 Hz), 7.1-7.4(5H, m) and 10.89(1H, s); MS: m/z 204(M^+), 100(base peak); *Anal.* Calcd. for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71; S, 15.70; Found: C, 64.74; H, 5.78; N, 13.53; S, 15.42.

1-Cyclohexylimidazole-2-thione, Colorless needles (benzene), mp. 175-176°C; lit. [3b] mp. 173-174°C; IR: 3168, 3112, 3028, 2938, 2860, 1578, 1488, 1449, 1422, 1389, 1290, 1257, 786, 723, and 672 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.1-2.2(10H, m), 4.64(1H, m), 6.73(2H, m), and 10.94(1H, s); MS: m/z 182(M^+), 100(base peak); *Anal.* Calcd. for $C_9H_{14}N_2S$: C, 59.30; H, 7.74; N, 15.37; S, 17.59; Found: C, 59.38; H, 7.75; N, 15.12; S, 17.31.

1-Isobutylimidazole-2-thione, Colorless prisms (benzene), mp. 140.5-141.5°C; lit. [3b] mp. 137-138°C; IR: 3142, 3028, 2968, 2938, 1578, 1488, 1458, 1419, 1383, 1359, 1338, 1275, 1254, 1155, 1113, 1095, 1029, 921, 780, 753, 732, 681, and 531 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.84(6H, d, J=6.4 Hz), 2.15(1H, m), 3.72(2H, d, J=7.6 Hz), 6.88(1H, m), 7.05(1H, m), and 12.04(1H, s); MS: m/z 156(M^+), 100(base peak); *Anal.* Calcd. for $C_7H_{12}N_2S$: C, 53.81; H, 7.74; N, 17.93; S, 20.52; Found: C, 53.67; H, 7.75; N, 17.65; S, 20.41.

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