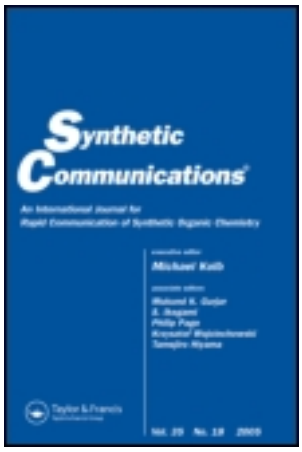

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AN EFFICIENT SOLID-STATE METHOD FOR THE PREPARATION OF ACYL THIOSEMICARBAZIDES

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AN EFFICIENT SOLID-STATE METHOD FOR THE PREPARATION OF ACYL THIOSEMICARBAZIDES

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ABSTRACT

Solid-state syntheses of acyl thiosemicarbazides are reported for the first time. Eleven acyl thiosemicarbazides have been synthesized at room temperature in excellent yields (84.5 ~ 91.0%). Among them, eight compounds **3a, 3d, 3e, 3g–k** are new. The reaction proves to be extremely simple and highly efficient (in 6 ~ 18 min).

Acyl thiosemicarbazide compounds exhibit various kinds of biological activities such as antiviral and antifungal.[1] They can be used as insecticides, herbicides and plant-growth regulators.[2] Many of them have potential medical usage[3] and some have been tried for the antituberculosis[4] and restraining central nerve.[5] Several methods have been developed for the synthesis of these compounds. The synthesis is usually carried out in solution, requiring large amounts of volatile and poisonous solvent,[6] needing complicated heat-

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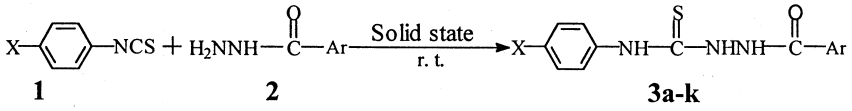
ing and stirring apparatus and long reaction times. Herein we describe a new and efficient method for synthesis of acyl thiosemicarbazides – solid-state synthesis.

Solid-state organic synthesis has extensive applications. It has many advantages over conventional solution phase synthesis such as high efficiency and selectivity, easy separation and purification of products, mild reaction conditions, and environmental acceptability.[7] All of these benefits are in accordance with the requests of green production, saving-energy and high efficiency. There are a variety of organic syntheses which involve solid-state reactions.[8–11] But the addition of acylhydrazine to aryl isothiocyanates has not yet been reported.

We have successfully synthesized eleven acyl thiosemicarbazides **3a–k** in excellent yields by the solid-state reaction of **1** and **2** (Scheme). No solvent or catalyst of complicated glassware is involved, the reaction is performed in an agate mortar by grinding the solids together at room temperature in 6 ~ 18 min. The structures of the products were characterized by IR, ^{1}H NMR, MS and Elemental analysis.



1 **2** **3a-k**

Scheme.

EXPERIMENTAL

Melting points were determined with a Kofler micro melting point apparatus and were uncorrected. IR spectra were recorded on a SP3-300 spectrophotometer in KBr. ^{1}H NMR spectra were measured on a FT-80A spectrometer using TMS as internal standard and $(CD_3)_2CO$ as solvent. Elemental analyses were performed on a Carlo-Erba 1102 elemental analyzer. Mass spectra were obtained on a KRATOS-AEI-MS50.

General procedure: A mixture of aryl isothiocyanate **1** (1 mmol) and acylhydrazine **2** (1 mmol) was ground thoroughly in an agate mortar. The mixture began to soften and melt in 1 ~ 2 minutes. Grinding was continued until the mixture became into solid again. The reaction was monitored by TLC. When the reaction was completed (6 ~ 18 min), the crude products was recrystallized from ethanol. Dryness *in vacuo* gave the pure products.

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Table. Solid-State Preparation of Acyl Thiosemicarbazides

Product	X	Ar	Reaction Time (min)	m.p. (°C)	Yield (%)
3a	Cl	C_6H_5	7	188 ~ 190	89.1
3b	Br	C_6H_5	10	183.5 ~ 184.5	86.5
3c	EtO	C_6H_5	6	181 ~ 183	91.0
3d	Cl	3-Cl C_6H_4	9	186.5 ~ 187.5	87.2
3e	Br	3-Cl C_6H_4	8	190 ~ 191	88.7
3f	EtO	3-Cl C_6H_4	11	174 ~ 176	84.7
3g	Cl	1-$C_{10}H_7CH_2$	8	174.5 ~ 176	85.0
3h	Br	1-$C_{10}H_7CH_2$	7	180 ~ 181	90.7
3i	EtO	1-$C_{10}H_7CH_2$	18	177 ~ 179	90.3
3j	Cl	$C_6H_5OCH_2$	16	181 ~ 183	86.9
3k	Br	$C_6H_5OCH_2$	17	188.5 ~ 190	84.5

All the compounds gave satisfactory analytical and spectral data:

1-Benzoyl-4-p-chlorophenyl thiosemicarbazide 3a: IR (KBr)/cm^{-1}: 3357, 3187, 3031, 1673, 1600, 1509, 1400, 1255, 833, 779, 690; ^{1}H NMR δ: 7.29 ~ 8.00 (m, 9H, ArH), 8.94 (s, 1H, NH), 9.60 (s, 1H, NH), 9.84 (s, 1H, NH); Anal. Calcd. for $C_{14}H_{12}ClN_3OS$: C, 54.99; H, 3.93; N, 13.75. Found: C, 54.78; H, 3.61; N, 13.57.

1-Benzoyl-4-p-bromophenyl thiosemicarbazide 3b: IR (KBr)/cm^{-1}: 3312, 3271, 3210, 3030, 1668, 1634, 1578, 1221, 825, 711, 687; ^{1}H NMR δ: 7.45 ~ 8.00 (m, 9H, ArH), 8.97 (s, 1H, NH), 9.60 (s, 1H, NH), 9.85 (s, 1H, NH); Anal. Calcd. for $C_{14}H_{12}BrN_3OS$: C, 48.00; H, 3.43; N, 12.00. Found: C, 48.31; H, 3.61; N, 11.89. MS (m/z): 351(M^+), 215, 213, 173, 171, 145, 134(B), 105, 77.

1-Benzoyl-4-p-ethoxyphenyl thiosemicarbazide 3c: IR (KBr)/cm^{-1}: 3320, 3276, 3200, 3035, 1670, 1635, 1590, 1545, 1230, 830, 770, 685; ^{1}H NMR δ: 1.34 (t, 3H, CH_3), 4.01 (q, 2H, CH_2), 6.83 ~ 8.01 (m, 9H, ArH), 8.74 (s, 1H, NH), 9.37 (s, 1H, NH), 9.79 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{17}N_3O_2S$: C, 60.95; H, 5.40; N, 13.33. Found: C, 60.69; H, 5.61; N, 13.37.

1-m-Chlorobenzoyl-4-p-chlorophenyl thiosemicarbazide 3d: IR (KBr)/cm^{-1}: 3318, 3215, 3153, 3033, 1671, 1638, 1620, 1546, 1209, 822, 735, 673; ^{1}H NMR δ: 7.32 ~ 7.99 (m, 8H, ArH), 8.98 (s, 1H, NH), 9.61 (s, 1H, NH), 9.96 (s, 1H, NH); Anal. Calcd. for $C_{14}H_{11}Cl_2N_3OS$: C, 49.41; H, 3.24; N, 12.35. Found: C, 49.78; H, 3.61; N, 12.67. MS (m/z): 341(M^+), 171, 169(B), 139, 137, 111, 75.

1-m-Chlorobenzoyl-4-p-bromophenyl thiosemicarbazide 3e: IR (KBr)/cm^{-1}: 3317, 3213, 3151, 3075, 1671, 1638, 1622, 1546, 1211, 819, 770, 673; ^{1}H NMR δ: 7.46 ~ 7.98 (m, 8H, ArH), 8.99 (s, 1H, NH), 9.61 (s, 1H, NH),

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9.97 (s, 1H, NH); Anal. Calcd. for $C_{14}H_{11}BrClN_3OS$: C, 43.69; H, 2.86; N, 10.92. Found: C, 43.78; H, 2.61; N, 10.77.

1-m-Chlorobenzoyl-4-p-ethoxyphenyl thiosemicarbazide 3f: IR (KBr)/cm^{-1}: 3318, 3220, 3150, 3030, 2980, 2920, 1670, 1640, 1620, 1550, 1215, 825, 770, 680; ^{1}H NMR δ: 1.32 (t, 3H, CH_3), 4.01 (q, 2H, CH_2), 6.83 ~ 7.99 (m, 8H, ArH), 8.77 (s, 1H, NH), 9.39 (s, 1H, NH), 9.92 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{16}ClN_3O_2S$: C, 54.94; H, 4.58; N, 12.02. Found: C, 54.69; H, 4.61; N, 12.37.

1-(1-Naphthoacetyl)-4-p-chlorophenyl thiosemicarbazide 3g: IR (KBr)/cm^{-1}: 3316, 3290, 3213, 3035, 1681, 1652, 1619, 1542, 1210, 832, 785; ^{1}H NMR δ: 4.13 (s, 2H, CH_2), 7.30 ~ 8.15 (m, 11H, ArH), 8.91 (s, 1H, NH), 9.20 (s, 1H, NH), 9.40 (s, 1H, NH); Anal. Calcd. for $C_{19}H_{16}ClN_3OS$: C, 61.71; H, 4.33; N, 11.37. Found: C, 61.31; H, 4.31; N, 11.59.

1-(1-Naphthoacetyl)-4-p-bromophenyl thiosemicarbazide 3h: IR (KBr)/cm^{-1}: 3315, 3287, 3210, 3034, 1680, 1650, 1620, 1545, 1213, 820, 769, 675; ^{1}H NMR δ: 4.13 (s, 2H, CH_2), 7.45 ~ 8.15 (m, 11H, ArH), 8.94 (s, 1H, NH), 9.21 (s, 1H, NH), 9.46 (s, 1H, NH); Anal. Calcd. for $C_{19}H_{16}BrN_3OS$: C, 55.07; H, 3.89; N, 10.14. Found: C, 55.31; H, 4.01; N, 10.29.

1-(1-Naphthoacetyl)-4-p-ethoxyphenyl thiosemicarbazide 3i: IR (KBr)/cm^{-1}: 3272, 3190, 3046, 3013, 2981, 2929, 1670, 1654, 1600, 1538, 1243, 820, 782; ^{1}H NMR δ: 1.34 (t, 3H, CH_3), 4.01 (q, 2H, CH_2), 4.13 (s, 2H, CH_2), 6.82 ~ 8.17 (m, 11H, ArH), 8.70 (s, 1H, NH), 8.99 (s, 1H, NH), 9.41 (s, 1H, NH); Anal. Calcd. for $C_{21}H_{21}N_3O_2S$: C, 66.49; H, 5.54; N, 11.08. Found: C, 66.31; H, 5.50; N, 11.29; MS (m/z): 380(M^+), 179, 150(B), 141, 115, 65.

1-p-Phenoxyacetyl-4-p-chlorophenyl thiosemicarbazide 3j: IR (KBr)/cm^{-1}: 3265, 3200, 3099, 2944, 1701, 1597, 1543, 1223, 825, 756, 689; ^{1}H NMR δ: 4.66 (s, 2H, CH_2), 6.97 ~ 7.57 (m, 9H, ArH), 8.92 (s, 1H, NH), 9.39 (s, 1H, NH), 9.74 (s, 1H, NH); Anal. Calcd. for $C_{15}H_{14}ClN_3O_2S$: C, 53.65; H, 4.17; N, 12.52. Found: C, 53.31; H, 4.50; N, 12.09; MS (m/z): 335(M^+), 171, 169(B), 127, 111, 94, 77, 75.

1-p-Phenoxyacetyl-4-p-bromophenyl thiosemicarbazide 3k: IR (KBr)/cm^{-1}: 3264, 3210, 3094, 2998, 2941, 1701, 1596, 1543, 1222, 836, 756, 689; ^{1}H NMR δ: 4.65 (s, 2H, CH_2), 6.97 ~ 7.50 (m, 9H, ArH), 8.92 (s, 1H, NH), 9.39 (s, 1H, NH), 9.75 (s, 1H, NH); Anal. Calcd. for $C_{15}H_{14}BrN_3O_2S$: C, 47.37; H, 3.68; N, 11.05. Found: C, 47.31; H, 3.50; N, 11.39.

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