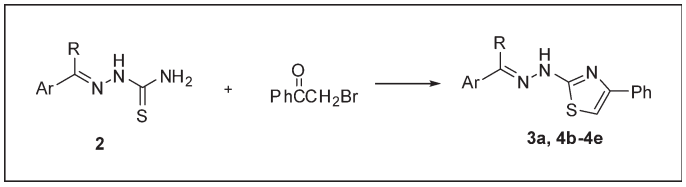
A Convenient and Efficient Synthesis of Heteroaromatic Hydrazone Derivatives *via* Cyclization of Thiosemicarbazone with ω-Bromoacetophenone

Weiwei Liu,[a]* Chuanzhou Tao,[a] Lijuan Tang,[a] Jie Li,[a] Yan Jin,[a] Yueqiang Zhao,[a] and Hongwen Hu[b]

[a]School of Chemical Engineering, Huaihai Institute of Technology, Lianyungang 222005, People's Republic of China
[b]Department of Chemistry, Nanjing University, Nanjing 210093, People's Republic of China
*E-mail: liuww323@yahoo.com.cn

Received March 19, 2010
DOI 10.1002/jhet.585
Published online 22 December 2010 in Wiley Online Library (wileyonlinelibrary.com).



The synthesis of hydrazone derivatives containing thiazole unit was achieved with condensation of thiosemicarbazones and ω-bromoacetophenone at room temperature. This mild, convenient, and efficient method affords the desired products with good to excellent yields. Their structures have been determined by X-ray diffractional analysis, ^{1}H-NMR, MS, elemental analysis, and IR. Thiosemicarbazones were prepared by the condensation of thiosemicarbazide with aldehydes or ketones.

J. Heterocyclic Chem., **48**, 361 (2011).

INTRODUCTION

Thiosemicarbazones and their derivatives are important compounds in organic and medicinal chemistry due to their biological properties including antitumor [1], antifungal [2], antibacterial [3], antimalarial [4], antifilarial [5], antiviral, and anti-HIV activities [6]. Thiosemicarbazones, especially those derived from heteroaromatic aldehydes or ketones have been extensively studied. It is found that their structural pi-delocalization of charge and configurational flexibility of their molecular chain can give rise to a variety of reaction manners.

As part of our studies on thiocarbonyl chemistry [7], the reactivity of heteroaromatic aldehyde- and ketone-derived thiosemicarbazones were further investigated. Chemical compounds with biological activity are often derived from heterocyclic structures. Heterocycles are an important class of scaffolds that are found in natural products such as vitamins, hormones, antibiotics, as well as pharmaceuticals, herbicides, and dyes. Herein, we report an efficient and convenient method to synthesize a new class of thiosemicarbazones that contain thiazole heterocyclic ring. These novel compounds were expected to exhibit biological activity in the near future. The structures of products have also been fully characterized by infrared spectroscopy (IR), ^{1}H nuclear magnetic resonance (^{1}H-NMR), mass spectrometry (MS), elemental analysis, and single-crystal X-ray diffraction analysis.

RESULTS AND DISCUSSION

Initially, thiosemicarbazones **2a** were synthesized by treating heterocyclic thioaldehydes **1a** with potassium hydroxide and an equimolar quantity of thiosemicarbazide in the cosolvent of anhydrous ethanol and dimethylsulfoxide (DMSO) [8]. The desired thiosemicarbazones **2b**–**2e** also can be readily formed under the acid or neutral condition. The results are summarized in Table 1.

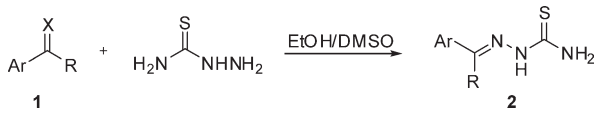
The structures of **2a**–**2e** were unambiguously characterized by spectroscopy (^{1}H-NMR, IR, and MS), elemental analysis, and further confirmed by X-ray diffractional analysis [9] of **2a**. The Oak Ridge Thermal Ellipsoid Plot (ORTEP) drawing and cell packing diagram are given in Figure 1.

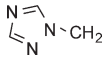
Subsequently, we treat heteroaromatic thiosemicarbazones **2a** with ω-bromoacetophenone in anhydrous ethanol. To our surprise, a novel compound (**3a**) with thiazole scaffold was formed. The reaction proceeds smoothly at room temperature and good yield (62%) was obtained. Single-crystal X-ray diffraction analysis [10] of **3a** was measured, and the ORTEP drawing and cell packing diagram are given in Figure 2.

Then, we examine whether the same reaction system can be applied to other heteroaromatic thiosemicarbazones (entries 2–5). It is found that both heteroaromatic aldehyde-derived and heteroaromatic ketone-derived thiosemicarbazones can be smoothly converted to the desired products with good to excellent yields (61–90%). The results were summarized in Table 2. It is

Table 1

Results of reactions of thiosemicarbazide with aldehydes, thioaldehydes, and ketones.



Entry	Ar	R	X	Solvent	Time (h)	Product	Yield (%)
1	2-Phenylindolizin-3-yl	H	S	EtOH/DMSO	6	**2a**	78
2	Furan-2-yl	H	O	EtOH/H_2O	2	**2b**	70
3	Thiophen-2-yl	H	O	EtOH/H_2O	5	**2c**	73
4	Indol-3-yl	H	O	EtOH/H_2O	3	**2d**	88
5	Phenyl		O	EtOH	4	**2e**	70

noteworthy that the present reaction was accomplished under mild conditions and the method is operationally simple with satisfactory yields. The structures of **3a, 4b–4e** have been characterized by spectroscopic (^{1}H-NMR, IR, and MS) and elemental analysis.

A plausible mechanism was proposed in Scheme 1. The bromine of ω-bromoacetophenone was substituted to form imide salt **5**. The protolysis reaction of **5** gave **6** followed by cyclization leading to 4-hydroxyl-4,5-dihydrothiazole salt **7**. The salt releases H_2O to afford thiazole salt **3a** and **4** followed by losing HBr to form thiazole ring. Since indolizinyl moiety has the strong conjugation ability, 3-formyl-2-phenylindolizine thiosemicarbazone (**2a**) can react with ω-bromoacetophenone to afford thiazole salt **3a**. When referred to other thiosemicarbazone (**2b–2e**), the final step is to release HBr to give products (**4b–4e**) with thiazole rings.

To conclude, in the present study, we report a convenient and efficient method to synthesize a series of novel thiosemicarbazone derivatives that contain thiazole heterocyclic ring. Given the fact that many thiosemicarbazone derivatives have exhibited biological activity, we anticipate that these new compounds described in the present report would be valuable for pharmaceutical research.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Nicolet FTIR 5DX spectrometer in KBr with absorption in cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker ACF-300 spectrometer, *J* values are in hertz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane. Mass spectra were obtained on a ZAB-HS mass spectrometer at 70 eV. Elemental analytical were performed on a Foss Heraeus CHN-O-Rapid analyzer.

Preparation of 3-formyl-2-phenylindolizine thiosemicarbazone (2a). A solution of 2-phenyl-3-thioformylindolizine (**1a**; 0.24 g, 1 mmol) and thiosemicarbazide (0.09 g, 1 mmol) in anhydrous ethanol (50 mL) was stirred, after adding potassium hydroxide (0.06 g, 1.1 mmol), DMSO (5 mL) was added dropwise. The mixture was refluxed at 80°C for 6 h [monitored by thin layer chromatography (TLC)], the resulting mixture was cooled and poured into ice water, filtered, purified by alumina chromatography eluted with the mixture of petroleum ether and ethyl acetate in gradient to afford **2a**.

General procedure for preparation of thiosemicarbazone (2b–2d). 'A solution of 2-formylfuran (**1b**; 0.29 g, 3 mmol) and thiosemicarbazide (0.27 g, 3 mmol) in 50% ethanol (20 mL) was stirred, 0.8-mL glacial acetic acid was added. The mixture was refluxed at 80°C for 2 h (monitored by TLC), the resulting mixture was cooled and poured into ice water, filtered, purified by recrystallization from anhydrous ethanol to afford **2b**. Under

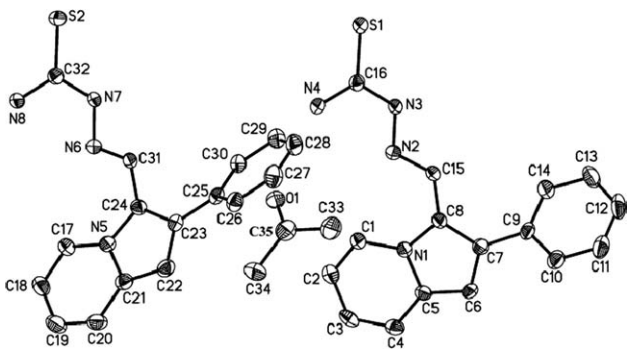


Figure 1. Molecular structure of **2a**.

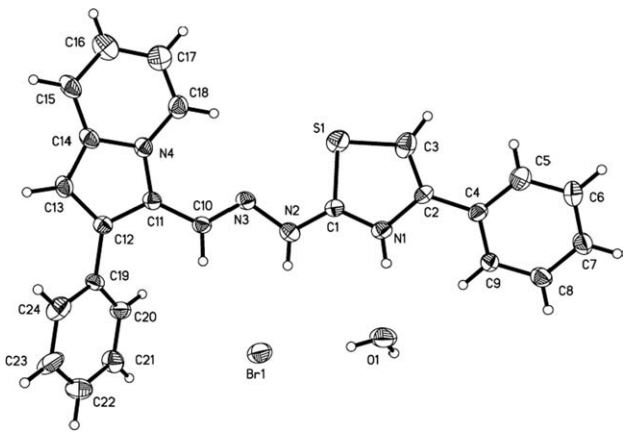
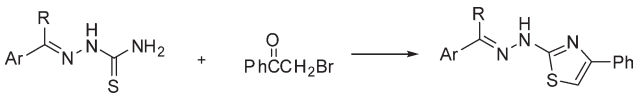


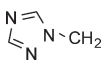
Figure 2. Molecular structure of **3a**.

Table 2

Reactions of heteroaromatic thiosemicarbazones **2** with ω-bromoacetophenone.



2 **3a, 4b-4e**

Entry	Ar	R	Time (min)	Product	Yield (%)
1	2-Phenylindolizin-3-yl	H	12	**3a**	62
2	Furan-2-yl	H	30	**4b**	87
3	Thiophen-2-yl	H	20	**4c**	66
4	Indol-3-yl	H	30	**4d**	90
5	Phenyl		30	**4e**	61

these conditions, reaction of **1b**–**1d** was similarly conducted to give the corresponding thiosemicarbazone **2b**–**2d**.

1-Phenyl-2-[1,2,4]triazol-1-ylethanone thiosemicarbazone (2e). A solution of 1-phenyl-2-[1,2,4]triazol-1-ylethanone (0.56 g, 3 mmol) and thiosemicarbazide (0.27 g, 3 mmol) in anhydrous ethanol (20 mL) was stirred, 0.2-mL glacial acetic acid and catalyst levels pyridine was added. The mixture was refluxed at 80°C for 4 h (monitored by TLC), the resulting mixture was cooled and poured into ice water, filtered, purified by recrystallization from anhydrous ethanol to afford **2e**.

General procedure for the cyclization of 2 and ω-bromoacetophenone to prepare 3a or 4b–4e. A solution of 2-phenyl-3-thioformylindolizine thiosemicarbazone **(2a**; 0.12 g, 0.40 mmol), ω-bromoacetophenone (0.085 g, 0.40 mmol) in anhydrous ethanol (10 mL) was stirred at room temperature, until all the thiosemicarbazone had disappeared (monitored by TLC). The deposit was filtered, purified by recrystallization from 95% ethanol to afford **3a**. Under these conditions, reaction of **2b**–**2e** was similarly conducted to give the corresponding cyclization compound **4b**–**4e**.

3-Formyl-2-phenylindolizine thiosemicarbazone (2a). Yellow crystals, Yield 78%, m.p. 155°C; IR (KBr): 3510, 3384, 3232, 3139, 3027.8, 1600, 1583, 1537, 1500, 1454, 1096, 834 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.41 (br, s, 1H, —NH_2), 6.67 (s, 1H, indolizin-3-yl C_1—H), 6.86–6.90 (m, 2H, indolizin-3-yl C_6—H, —NH_2), 7.04–7.10 (m, 1H, indolizin-3-yl C_7—H), 7.44–7.58 (m, 6H, Ph, indolizin-3-yl C_8—H), 8.10 (s, 1H, =CH—), 9.14 (s, 1H, —NH—), 9.21 (d, J = 7.0 Hz, 1H, indolizin-3-yl C_5—H). Anal. Calcd for $C_{16}H_{14}N_4S$: C, 65.31; H, 4.76; N, 19.05. Found: C, 65.45; H, 4.95; N, 19.10. MS (EI): *m*/*z* 276 (58.9), 249 (24.7), 218 (51.3), 193 (100), 165 (35.3), 115 (29.6), 83 (30.8), 51 (28.9).

2-Formylfuran thiosemicarbazone (2b). Yellowish brown crystals, yield 70%, m.p. 154–156°C (lit. 152–154°C) [8].

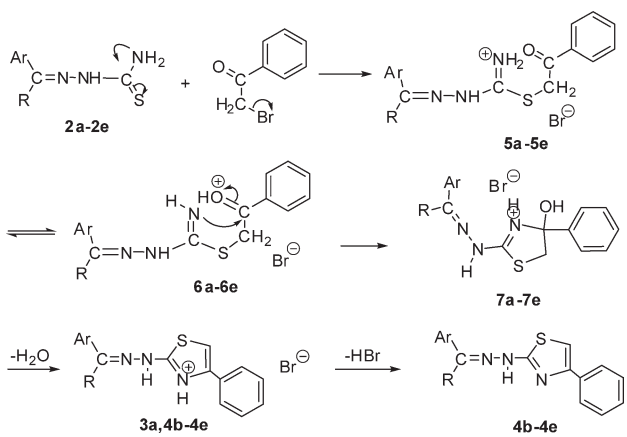
2-Formylthiophene thiosemicarbazone (2c). Light brown crystals, yield 73%, m.p. 184–186°C (lit. 185–186°C) [8].

3-Formyl-1H-indole thiosemicarbazone (2d). Light pink crystals, yield 88%, m.p. 232–234°C; IR (KBr): 3448, 3311, 3230, 3145, 3039, 1613, 1582, 1550, 1518, 1441, 1200, 751 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.10–7.21 (m, 2H, indol-3-yl C_6-H, indol-3-yl C_7—H), 7.42 (br, s, 1H, —NH_2), 7.43 (d, J = 7.9 Hz, 1H, indol-3-yl C_8—H), 7.82 (d, J = 2.7 Hz, 1H, indol-3-yl C_2—H), 8.03 (br, s, 1H, —NH_2), 8.23 (d, J = 7.7 Hz, 1H, indol-3-yl C_5—H), 8.31(s, 1H, =CH—), 11.18 (s, 1H, —NH—), 11.61 (s, 1H, indol-3-yl nitrogen proton). Anal. Calcd for $C_{10}H_{10}N_4S$: C, 55.04; H, 4.59; N, 25.69. Found: C, 55.10; H, 4.55; N, 25.62. MS (EI): *m*/*z* 218 (M^+, 2.4), 201 (16), 143 (61.2), 142 (100), 115 (28.9), 89 (10.9).

1-Phenyl-2-[1,2,4]triazol-1-ylethanone thiosemicarbazone (2e). Colorless crystals, yield 70%, m.p. 157–159°C ; IR (KBr): 3373, 3264, 3173, 3073, 2986, 1644, 1619, 1603, 1510, 1492, 1448, 1270, 844, 745, 676 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 5.73 (s, 2H, —CH_2—), 7.37–7.95 (m, 5H, PhH), 8.11 (s, 1H, —NH_2), 8.52 (s, 1H, 1*H*-1, 2, 4-triazol-1-yl proton), 8.65 (s, 1H, —NH_2), 8.68 (s, 1H, 1*H*-1, 2, 4-triazol-1-yl proton), 10.96 (s, 1H, —NH—). Anal. Calcd for $C_{11}H_{12}N_6S$: C, 50.77; H, 4.62; N, 32.31. Found: C, 50.85; H, 4.67; N, 32.30. ; MS (EI): *m*/*z* 243 (1.4), 178 (15.9), 103 (100), 77 (44.2), 69 (10.5).

N-(4-phenyl-thiazol-2-yl)-3-formyl-2-phenylindolizine hydrazone hydrobromic acid (3a). Green crystals, yield 62%, m.p. 122–124°C; IR (KBr): 3333, 2853, 1625, 1590, 1533, 1496, 1456, 764, 697 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.72 (s, 1H, indolizin-3-yl C_1—H), 6.90–7.01 (m, 1H, indolizin-3-yl C_6—H), 7.10–7.21 (m, 1H, indolizin-3-yl C_7—H), 7.37–7.88 (m, 12H, indolizin-3-yl C_8—H, phenyl and thiazole ring proton); 8.41 (s, 1H, =C—H), 9.31 (d, J = 8.2 Hz, 1H, indolizin-3-yl C_5—H), 12.61 (s, 1H, —NH—), 13.87 (s, 1H, —N^+H—). Anal. Calcd for $C_{24}H_{21}BrN_4OS$: C, 58.42; H, 4.26; N, 11.36. Found:

Scheme 1



C, 58.50; H, 4.42; N, 11.26. MS (EI): *m/z* 394 [(M-HBr-H_2O)$^+$, 2.9], 219 (92), 218 (100), 192 (2.2), 176 (96.6), 134 (56.6).

N-(4-phenyl-thiazol-2-yl)-2-formylfuran hydrazone (4b). Brownish yellow crystals, yield 87%, m.p. 136–138°C; IR (KBr): 3117, 3141, 3065, 1619, 1603, 1561, 1486, 760, 691 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.59–6.62 (m, 1H, furan-2-yl C_4—H), 6.81 (d, J = 3.3 Hz, 1H, furan-2-yl C_3—H), 7.23–7.93 (m, 9H, thiazole ring and phenyl proton, furan-2-yl C_5—H, =C—H, —NH—). Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.45; H, 4.09; N,15.61. Found: C, 62.53; H, 4.05; N,15.77. MS (EI): *m/z* 269 (M^+, 16.8), 176 (100), 134 (62.6).

N-(4-phenyl-thiazol-2-yl)-2-formylthiophene hydrazone (4c). Light brown crystals, yield 66%, m.p. 202–203°C; IR (KBr): 3302, 3099, 3055, 1602, 1561, 1521, 1505, 1490, 768, 748, 740, 722, 706, 683 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.80 (s, 1H, thiazole ring proton), 7.00–7.90 (m, 8H, thiophen-2-yl and phenyl proton), 7.97 (s, 1H, —CH=N—), 8.20 (br, s, 1H, —NH—). Anal. Calcd for $C_{14}H_{11}N_3S_2$: C, 58.95; H, 3.86; N, 14.74.Found: C, 59.01; H, 3.96; N, 14.65. MS (EI): *m/z* 285 (M^+, 15.8), 176 (100), 134 (83.5), 110 (4.4), 77 (2.5).

N-(4-phenyl-thiazol-2-yl)-2-formyl-1H-indole hydrazone (4d). Light purple crystals, yield 90%, m.p. 185–187°C; IR (KBr): 3292, 3103, 2943, 1625, 1608, 1574, 1531, 1491, 749, 735 675 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.15–7.52 (m, 8H, thiazole ring and phenyl proton, indol-3-yl C_6—H, indol-3-yl C_7—H), 7.78 (s, 1H, —NH—), 7.85–7.95 (m, 2H, indol-3-yl C_8—H, indol-3-yl C_2—H), 8.23–8.35 (m, 2H, indol-3-yl C_5—H, =CH—), 11.61 (s, 1H, indol-3-yl nitrogen proton). Anal. Calcd for $C_{18}H_{14}N_4S$: C, 67.92; H, 4.40; N, 17.61. Found: C, 67.93; H, 4.32; N, 17.66. MS (EI): *m/z* 318 (M^+, 0.5), 176 (100), 142 (59.6), 134 (38.4), 115 (7.4), 89 (5.2).

N-(4-phenyl-thiazol-2-yl)-ω-(1, 2, 4-triazol-1-yl)acetophenone hydrazone (4e) Light yellow crystals, yield 61%, m.p. 212–214°C; IR (KBr): 3165, 3096, 3081, 2656, 1598, 1583, 1503, 1444, 749, 688 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 5.74 (s, 2H, —CH_2—); 7.33–7.89 (m, 11H, thiazole ring and phenyl proton), 7.97 (s, 1H, 1*H*-1, 2, 4-triazol-1-yl proton), 8.74 (s, 1H, 1*H*-1, 2, 4-triazol-1-yl proton). Anal. Calcd for $C_{19}H_{16}N_6S$: C, 58.95; H, 3.86; N, 14.74. Found: C, 59.01; H, 3.96; N, 14.65. MS (EI): *m/z* 291 (22.7), 262 (18.8), 176 (9.4), 134 (59.9), 103 (100), 77 (66.5), 69 (13.9).

Acknowledgments. The authors are grateful to the National Natural Science Foundation of China (No. 20672090), the Six Kinds of Professional Elite Foundation of Jiangsu Province (No. 07-A-024), the Science and Technology Critical Project Foundation of Lianyungang Municipality (CG0803-2), and the Natural Science Foundation of Jiangsu Education Department (08KJB150002).

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[9] Crystal data for **2a**: $2(C_{16}H_{14}N_4S)\cdot C_2H_6CO$; M = 646, Yellow single crystals, 0.20 × 0.20 × 0.30 mm^3, triclinic, space group $P1$, a = 11.572 (8), b = 11.845 (8), c = 13.173 (8) Å, α = 92.56 (3), β = 110.61 (4), γ = 102.57 (4)°, V = 1635 (2) Å^3, Z = 2, D_c = 1.318 mg m^{-3}. F (000) = 682, μ (MoKα) = 0.206 mm^{-1}. Intensity data were collected on Bruker SMART APEX II with graphite monochromated MoKα radiation (λ = 0.71073 Å) using ω scan mode with 1.9° < θ < 25.0°. 5671 unique reflections were measured and 4302 reflections with $I > 2\sigma(I)$ were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R = 0.0533 and wR = 0.1168.

[10] Crystal data for **3a**: $C_{24}H_{21}BrN_4OS$; M = 493, Blackish green single crystals, 0.42 × 0.36 × 0.20 mm^3, monoclinic, space group $P2_1/n$, a = 6.1679 (12), b = 11.1657 (18), c = 32.640 (4) Å, α = 90, β = 91.708 (2), γ = 90°, V = 2246.9 (6) Å^3, Z = 4, D_x = 1.459 mg m^{-3}. F (000) = 1008, μ (MoKα) = 1.946 mm^{-1}. Intensity data were collected on Bruker SMART APEX II with graphite monochromated MoKα radiation (λ = 0.71073 Å) using ω scan mode with. 1.93° < θ < 25.01°. 3904 unique reflections were measured and 2795 reflections with $I > 2\sigma(I)$ were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R = 0.0661 and wR = 0.1554.