Chemistry of Heterocyclic Compounds, Vol. 42, No. 4, 2006

SYNTHESIS OF NEW THIADIAZOLINE DERIVATIVES CONTAINING TRIAZOLYLMETHYL OR BENZOTRIAZOLYLMETHYL SUBSTITUENTS

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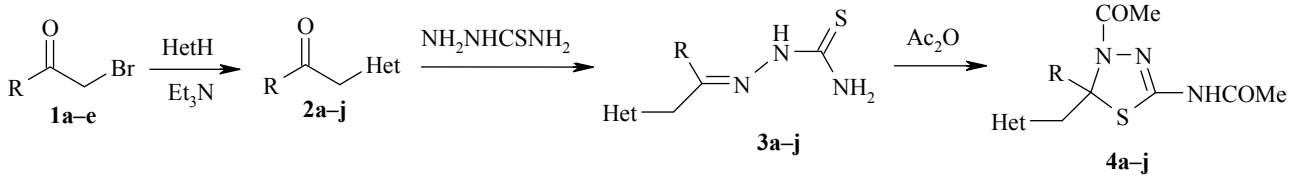
Some new thiosemicarbazones have been synthesized by condensation reaction of substituted 1-phenacyl-1,2,4-triazoles and -benzotriazoles with thiosemicarbazide, which underwent cyclization with acetic anhydride to give a series of substituted thiadiazoline derivatives in good yields. Their structures were confirmed by elemental analysis, IR, ^{1}H NMR, and MS.

Keywords: 1H-benzotriazole, thiadiazoline, 1H-1,2,4-triazole.

Heterocycles containing a triazole ring attract considerable attention because molecules with this structural fragment display a wide range of potent biological activities such as antihypertensive, antifungal, antibacterial, and anticonvulsant, as well as properties of plant growth regulators [1-6]. In addition, many substituted thiadiazoline derivatives show anti-HIV-1, insecticidal, and central nervous system inhibitor activities [7-9]. Therefore, we can enhance many physiological activities by combining the thiadiazoline moiety with triazole or benzotriazole systems. Although acylation of ketone thiosemicarbazones with acid anhydride has been reported as an efficient route to synthesize substituted 1,3,4-thiadiazolines [10], there are very few works on the synthesis of substituted thiadiazolines containing 1H-1,2,4-triazole or 1H-benzotriazole moieties. For this reason, we have efficiently synthesized a series of 4-acyl-2-acylamino-Δ^2-1,3,4-thiadiazoline derivatives containing 1H-1,2,4-triazolylmethyl or 1H-benzotriazolylmethyl substituents in the molecules.

Substituted ω-bromoacetophenones **1a-e,** ω-(1H-1,2,4-triazol-1-yl)aceto- phenones **2a-e,** and ω-(1H-benzotriazol-1-yl)acetophenones **2f-j** were obtained according to the literature [11, 12]. The treatment of **2a-j** with thiosemicarbazide in the presence of acetic acid yielded new thiosemicarbazones **3a-j**. Acylation of **3a-j** with acetic anhydride under reflux gave a series of substituted thiadiazoline derivatives **4a-j.**

The intermediates **3a-j** were substantiated by elemental analyses and IR spectra. The IR spectra of compounds **3a-j** revealed in each case absorption bands in the regions of 3395-3161, 1616-1604, 1276-1261 cm^{-1} corresponding to N–H, C=N, and C=S, respectively.



2-4 a R = Ph, **b** R = *p*-MeC_6H_4, **c** R = *p*-BrC_6H_4, **d** R = *p*-ClC_6H_4, **e** R = *p*-$MeOC_6H_4$, **f** R = Ph, **g** R = *p*-MeC_6H_4, **h** R = *p*-BrC_6H_4, **i** R = *p*-ClC_6H_4, **j** R = *p*-$MeOC_6H_4$; **2-4 a-e** Het = 1H-1,2,4-triazolyl, **f-j** Het = 1H-benzotriazolyl

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Chemistry and Chemical Engineering Institute of Xinjiang University, Urumqi 830046, P.R. China. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 4, 605-609, April, 2006. Original article submitted December 8, 2004.

The structure of the title compounds **4a-j** has been confirmed by elemental analysis, IR, ^{1}H NMR, and MS. The IR spectra of these compounds show C=C/C=N and C=O absorption bands between 1612-1491 and 1695-1647 cm^{-1}, respectively, and a broad band at 3219-3180 cm^{-1} due to N–H absorption.

In the nuclear magnetic resonance spectra the title compounds exhibited a broad singlet between δ 11.62-10.72 ppm due to N–H protons. The presence of multiplet signal at δ 8.60-6.93 ppm was assigned to the aromatic and heterocyclic protons, and the methylene groups appeared as a singlet at δ 4.81-6.10 ppm.

In the mass spectra $[M–H]^-$ the peaks of all the title compounds were obtained from ESI–MS, and the intensities of $[M–H]^-$ peaks are very strong.

EXPERIMENTAL

Melting points were recorded on a Mettler FP-5 capillary melting point apparatus and are uncorrected. Elemental analyses were recorded on a Perkin–Elmer 2400 element analyzer. IR spectra were measured as a potassium bromide pellet on a Biorad FT-40 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Inova-400 spectrometer (400 MHz) in $CDCl_3$ (**4a-e**) or DMSO-d_6 (**4f-j**) using TMS as an internal reference. Mass spectra were performed on an HP 1100-LC-MS (ESI).

Thiosemicarbazones 3a-j (General Procedure). A mixture of ω-(1H-1,2,4-triazol-1-yl)- acetophenone (**2a**) (0.01 mol), thiosemicarbazide (0.01 mol), ethanol (16 ml), H_2O (4 ml) and acetic acid (4 ml) was refluxed for 4 h, then allowed to cool. The solid product was collected and recrystallized from anhydrous ethanol to give **3a** as a white solid.

Other thiosemicarbazones were prepared analogously.

ω-(1H-1,2,4-Triazol-1-yl)acetophenone Thiosemicarbazone (3a). A white solid, yield 76.2%; mp 152.3-153.5°C. IR spectrum, ν, cm^{-1}: 3390, 3279, 3226 (NH_2, NH), 1613 (C=N), 1275 (C=S). Found, %: C 50.72; H 4.67; N 32.26. $C_{11}H_{12}N_6S$. Calculated, %: C 50.75; H 4.65; N 32.28.

ω-(1H-1,2,4-Triazol-1-yl)-*p*-methylacetophenone Thiosemicarbazone (3b). A white solid, yield 74.5%; mp 195.8-196.7°C. IR spectrum, ν, cm^{-1}: 3395, 3280, 3215 (NH_2, NH), 1604 (C=N), 1276 (C=S). Found, %: C 52.52; H 5.16; N 30.69. $C_{12}H_{14}N_6S$. Calculated, %: C 52.54; H 5.14; N 30.63.

ω-(1H-1,2,4-Triazol-1-yl)-*p*-bromoacetophenone Thiosemicarbazone (3c). A white solid, yield 74.8%; mp 216.4-217.2°C. IR spectrum, ν, cm^{-1}: 3389, 3280, 3221 (NH_2, NH), 1608 (C=N), 1274 (C=S). Found, %: C 38.97; H 3.26; N 24.74. $C_{11}H_{11}BrN_6S$. Calculated, %: C 38.95; H 3.27; N 24.77.

ω-(1H-1,2,4-Triazol-1-yl)-*p*-chloroacetophenone Thiosemicarbazone (3d). A white solid, yield 76.2%; mp 207.2-208.7°C. IR spectrum, ν, cm^{-1}: 3393, 3286, 3220 (NH_2, NH), 1605 (C=N), 1272 (C=S). Found, %: C 44.85; H 3.75; N 28.48. $C_{11}H_{11}ClN_6S$. Calculated, %: C 44.82; H 3.76; N 28.51.

ω-(1H-1,2,4-Triazol-1-yl)-*p*-methoxyacetophenone Thiosemicarbazone (3e). A white solid, yield 78.3%; mp 198.2-199.1°C. IR spectrum, ν, cm^{-1}: 3395, 3282, 3223 (NH_2, NH), 1605 (C=N), 1270 (C=S). Found, %: C 49.61; H 4.84; N 28.96. $C_{12}H_{14}ON_6S$. Calculated, %: C 49.64; H 4.86; N 28.94.

ω-(1H-Benzotriazol-1-yl)acetophenone Thiosemicarbazone (3f). A white solid, yield 72.6%; mp 176.7-178.1°C. IR spectrum, ν, cm^{-1}: 3344, 3264, 3168 (NH_2, NH), 1613 (C=N), 1265 (C=S). Found, %: C 58.08; H 4.57; N 27.02. $C_{15}H_{14}N_6S$. Calculated, %: C 58.04; H 4.55; N 27.08.

ω-(1H-Benzotriazol-1-yl)-*p*-methylacetophenone Thiosemicarbazone (3g). A white solid, yield 70.3%; mp 150.3-151.6°C. IR spectrum, ν, cm^{-1}: 3351, 3270, 3172 (NH_2, NH), 1615 (C=N), 1262 (C=S). Found, %: C 59.21; H 4.99; N 25.98. $C_{16}H_{16}N_6S$. Calculated, %: C 59.23; H 4.97; N 25.91.

ω-(1H-Benzotriazol-1-yl)-*p*-bromoacetophenone Thiosemicarbazone (3h). A white solid, yield 69.7%; mp 159.6-161.3°C. IR spectrum, ν, cm^{-1}: 3342, 3275, 3161 (NH_2, NH), 1615 (C=N), 1267 (C=S). Found, %: C 46.24; H 3.39; N 24.60. $C_{15}H_{13}BrN_6S$. Calculated, %: C 46.28; H 3.37; N 21.59.

ω-(1H-Benzotriazol-1-yl)-*p*-chloroacetophenone Thiosemicarbazone (3i). A white solid, yield 75.6%; mp 157.8-159.3°C. IR spectrum, ν, cm^{-1}: 3349, 3268, 3173 (NH_2, NH), 1616 (C=N), 1268 (C=S). Found, %: C 52.28; H 3.82; N 24.32. $C_{15}H_{13}ClN_6S$. Calculated, %: C 52.24; H 3.80; N 24.38.

ω-(1H-Benzotriazol-1-yl)-*p*-methoxyacetophenone Thiosemicarbazone (3j). A white solid, yield 70.6%; mp 187.2-189.1°C. IR spectrum, ν, cm^{-1}: 3357, 3276, 3162 (NH_2, NH), 1612 (C=N), 1261 (C=S). Found, %: C 56.47; H 4.73; N 24.65. $C_{16}H_{16}ON_6S$. Calculated, %: C 56.45; H 4.74; N 24.69.

Thiadiazolines 4a-e (General Procedure). A mixture of **3a** (5 mmol) and acetic anhydride (5 ml) was refluxed for 0.5 h. The solution was cooled, poured into ice water, neutralized with sodium hydroxide (2 M), and kept overnight at room temperature. The separated solid was filtered off, dried, washed with water, dried, and recrystallized from benzene/ethanol to give **4a** as a white powder solid. The syntheses of compounds **4b-e** were carried out by the same manner as **4a**.

2-Acetamido-4-acetyl-5-phenyl-5-(1H-1,2,4-triazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4a). A white solid, yield 74.3%; mp 238.5-239.1°C. IR spectrum, ν, cm^{-1}: 3215 (NH), 1692, 1651 (C=O), 1602, 1572, 1495 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.42 (1H, s, NH); 8.54 (1H, s, triazole $C_{(5)}H$); 8.00 (1H, s, triazole $C_{(3)}H$); 7.47-7.32 (5H, m, ArH); 5.75 (1H, d, *J* = 14.4, CH_2); 5.35 (1H, d, *J* = 14.4, CH_2); 2.18 (3H, s, $COCH_3$); 1.95 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 343 $[M–H]^-$ (100). Found, %: C 52.29; H 4.69; N 24.45. $C_{15}H_{16}N_6O_2S$. Calculated, %: C 52.31; H 4.68; N 24.40.

2-Acetamido-4-acetyl-5-(*p*-tolyl)-5-(1H-1,2,4-triazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4b). A white solid, yield 78.6%; mp 171.0-171.6°C. IR spectrum, ν, cm^{-1}: 3219 (NH), 1690, 1657 (C=O), 1607, 1568, 1497 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.80 (1H, s, NH); 8.23 (1H, s, triazole $C_{(5)}H$); 7.80 (1H, s, triazole $C_{(3)}H$); 7.21-7.06 (4H, m, ArH); 5.72 (1H, d, *J* = 14.4 Hz, CH_2); 4.81 (1H, d, *J* = 14.0, CH_2); 2.26 (3H, s, CH_3); 2.15 (3H, s, $COCH_3$); 1.94 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 357 $[M–H]^-$ (100). Found, %: C 53.65; H 5.07; N 23.43. $C_{16}H_{18}N_6O_2S$. Calculated, %: C 53.62; H 5.06; N 23.45.

2-Acetamido-4-acetyl-5-(4-bromophenyl)-5-(1H-1,2,4-triazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4c). A white solid, yield 77.9%; mp 235.0-236.5°C. IR spectrum, ν, cm^{-1}: 3210 (NH), 1695, 1649 (C=O), 1605, 1576, 1497 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.54 (1H, s, NH); 8.58 (1H, s, triazole $C_{(5)}H$); 8.03 (1H, s, triazole $C_{(3)}H$); 7.52-7.23 (4H, m, ArH); 5.77 (1H, d, *J* = 14.4, CH_2); 5.27 (1H, d, *J* = 14.4, CH_2); 2.20 (3H, s, $COCH_3$); 1.94 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 423 $[M–H+2]^-$ (95), 421 $[M–H]^-$ (100). Found, %: C 42.52; H 3.55; N 19.89. $C_{15}H_{15}BrN_6O_2S$. Calculated, %: C 42.56; H 3.57; N 19.85.

2-Acetamido-4-acetyl-5-(4-chlorophenyl)-5-(1H-1,2,4-triazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4d). A white solid, yield 73.1%; mp 235.1-236.8°C. IR spectrum, ν, cm^{-1}: 3213 (NH), 1686, 1647 (C=O), 1600, 1565, 1501 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.60 (1H, s, NH); 8.60 (1H, s, triazole $C_{(5)}H$); 8.08 (1H, s, triazole $C_{(3)}H$); 7.39-7.20 (4H, m, ArH); 5.80 (1H, d, *J* = 14.4, CH_2); 5.39 (1H, d, *J* = 14.4, CH_2); 2.21 (3H, s, $COCH_3$); 1.94 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 379 $[M–H+2]^-$ (36), 377 $[M–H]^-$ (100). Found, %: C 47.59; H 3.97; N 22.20. $C_{15}H_{15}ClN_6O_2S$. Calculated, %: C 47.56; H 3.99; N 22.18.

2-Acetamido-4-acetyl-5-(4-methoxyphenyl)-5-(1H-1,2,4-triazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4e). A white solid, yield 72.8%; mp 164.3-165.9°C. IR spectrum, ν, cm^{-1}: 3217 (NH), 1692, 1653 (C=O), 1610, 1574, 1492 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.92 (1H, s, NH); 8.36 (1H, s, triazole $C_{(5)}H$); 7.95 (1H, s, triazole $C_{(3)}H$); 7.23-6.93 (4H, m, ArH); 5.74 (1H, d, *J* = 14.4, CH_2); 4.87 (1H, d, *J* = 14.0, CH_2); 3.92 (3H, s, OCH_3); 2.17 (3H, s, $COCH_3$); 1.95 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 373 $[M–H]^-$ (100). Found, %: C 51.29; H 4.86; N 22.47. $C_{16}H_{18}N_6O_3S$. Calculated, %: C 51.33; H 4.85; N 22.45.

Thiadiazolines 4f-j (General Procedure). A mixture of **3f** (5 mmol) and acetic anhydride (5 ml) was refluxed for 0.5 h. A solid product appeared in the refluxing process and was collected after being cooled. The product was recrystallized from DMF/EtOH to give **4f** as a white powder solid. The syntheses of compounds **4g-j** were carried out by the same manner as **4f**.

2-Acetamido-4-acetyl-5-phenyl-5-(1H-benzotriazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4f). A white solid, yield 80.1%; mp 263.5-265.2°C. IR spectrum, ν, cm^{-1}: 3184 (NH), 1685, 1659 (C=O), 1600, 1569, 1491 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.15 (1H, s, NH); 8.08-7.35 (9H, m, ArH); 6.04 (1H, d,

J = 14.8, CH_2); 5.83 (1H, d, J = 14.4, CH_2); 2.14 (3H, s, $COCH_3$); 1.77 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 393 $[M–H]^-$ (100). Found, %: C 57.81; H 4.61; N 21.34. $C_{19}H_{18}N_6O_2S$. Calculated, %: C 57.85; H 4.60; N 21.31.

2-Acetamido-4-acetyl-5-(*p*-tolyl)-5-(1H-benzotriazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4g). A white solid, yield 82.4%; mp 272.1-273.5°C. IR spectrum, ν, cm^{-1}: 3188 (NH), 1680, 1648 (C=O), 1608, 1574, 1498 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.72 (1H, s, NH); 8.05-7.12 (8H, m, ArH); 5.98 (1H, d, J = 14.4, CH_2); 5.45 (1H, d, J = 14.0, CH_2); 2.23 (3H, s, CH_3); 2.10 (3H, s, $COCH_3$); 1.78 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 407 $[M–H]^-$ (100). Found, %: C 58.84; H 4.92; N 20.56. $C_{20}H_{20}N_6O_2S$. Calculated, %: C 58.81; H 4.94; N 20.57.

2-Acetamido-4-acetyl-5-(4-bromophenyl)-5-(1H-benzotriazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4h). A white solid, yield 74.5%; mp 283.8-284.6°C. IR spectrum, ν, cm^{-1}: 3180 (NH), 1689, 1652 (C=O), 1612, 1578, 1505 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.22 (1H, s, NH); 8.11-7.25 (8H, m, ArH); 6.05 (1H, d, J = 14.4, CH_2); 5.72 (1H, d, J = 14.4, CH_2); 2.15 (3H, s, $COCH_3$); 1.78 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 473 $[M–H+2]^-$ (94), 471 $[M–H]^-$ (100). Found, %: C 48.17; H 3.60; N 17.78. $C_{19}H_{17}BrN_6O_2S$. Calculated, %: C 48.21; H 3.62; N 17.75.

2-Acetamido-4-acetyl-5-(4-chlorophenyl)-5-(1H-benzotriazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4i). A white solid, yield 78.1%; mp 280.2-281.8°C. IR spectrum, ν, cm^{-1}: 3192 (NH), 1681, 1657 (C=O), 1602, 1574, 1495 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.26 (1H, s, NH); 8.14-7.18 (8H, m, ArH); 6.10 (1H, d, J = 14.4, CH_2); 5.87 (1H, d, J = 14.0, CH_2); 2.18 (3H, s, $COCH_3$); 1.78 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 429 $[M–H+2]^-$ (35), 427 $[M–H]^-$ (100). Found, %: C 53.22; H 4.01; N 19.56. $C_{19}H_{17}ClN_6O_2S$. Calculated, %: C 53.21; H 4.00; N 19.59.

2-Acetamido-4-acetyl-5-(4-methoxyphenyl)-5-(1H-benzotriazol-1-yl-methyl)-Δ^2-1,3,4-thiadiazoline (4j). A white solid, yield 73.6%; mp 257.6-258.0°C. IR spectrum, ν, cm^{-1}: 3181 (NH), 1690, 1655 (C=O), 1607, 1572, 1503 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.87 (1H, s NH); 8.10-6.96 (8H, m, ArH); 6.01 (1H, d, J = 14.4, CH_2); 5.56 (1H, d, J = 14.0, CH_2); 3.95 (3H, s, OCH_3); 2.13 (3H, s, $COCH_3$); 1.77 (3H, s, $NHCOCH_3$). Mass spectrum (ESI), *m/z* (I_{rel}, %): 423 $[M–H]^-$ (100). Found, %: C 56.56; H 4.73; N 19.84. $C_{20}H_{20}N_6O_3S$. Calculated, %: C 56.59; H 4.75; N 19.80.

This work was financially supported by the Natural Science Foundation in P. R. China.

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