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Convenient Synthesis of [1,2,4]Triazolo[4,3-*a*][1,3,5]triazin-5-amines, [1,2,4]Triazolo[4,3-*c*][1,3,5]thiadiazine-5-thiones, and [1,2,4]Triazolo[4,3-*c*][1,3,5]thiadiazin-5-imines from *N*-(4*H*-1,2,4-Triazol-3-yl) Carboximidates

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Abstract—The condensation of 4*H*-1,2,4-triazol-3-amine with ortho esters derived from acetic, propionic, and benzoic acids gave the corresponding *N*-(4*H*-1,2,4-triazol-3-yl) carboximidates which were treated with cyanamide, carbon disulfide, and sodium thiocyanate to afford 7-substituted [1,2,4]triazolo[4,3-*a*][1,3,5]triazin-5-amines, [1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazine-5-thiones, and [1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazin-5-imines, respectively. The structures of the synthesized compounds were confirmed by IR, ^{1}H and ^{13}C NMR, and mass spectra and elemental analyses.

Keywords: 1,2,4-triazol-3-amine, carboximidates, [1,2,4]triazolo[4,3-*a*]triazin-5-amines, [1,2,4]triazolo[4,3-*c*]-[1,3,5]thiadiazine-5-thiones, [1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazin-5-imines, ortho esters.

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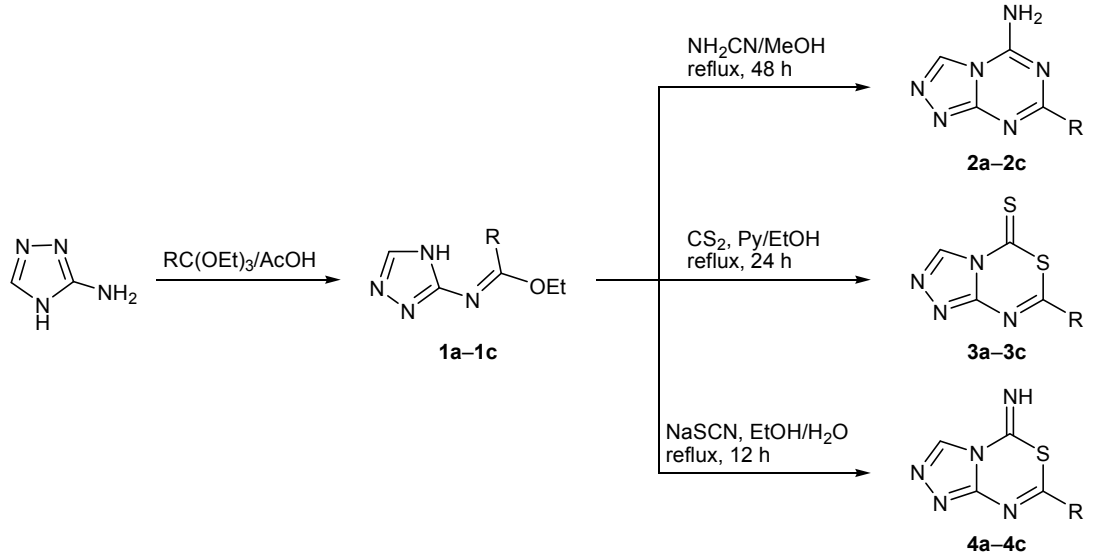
The design, synthesis, and production of compounds valuable as biological and therapeutic agents remain one of the main objectives of organic and medicinal chemistry. The importance of triazolotriazines is well recognized in the field of medicinal chemistry because these heterocycles are structurally related to purine and adenine [1, 2]. Triazolotriazines have been reported to possess different biological activities; in particular, herbicides [3], eosinophilia inhibitors [4], and antitumor agents have been found in the triazolotriazine series [5, 6]. Among triazole derivatives, triazolothiadiazines have received considerable attention due to their biological importance [7, 8].

Our recent interests were aimed at the synthesis and chemical properties of [1,2,4]triazolo[4,3-*a*][1,3,5]triazin-5-amines **2a**–**2c**, [1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazine-5-thiones **3a**–**3c**, and [1,2,4]triazolo[4,3-*c*]-[1,3,5]thiadiazin-5-imines **4a**–**4c**.

N-(4*H*-1,2,4-Triazol-3-yl) carboximidates **1a**–**1c** were synthesized by condensation of 4*H*-1,2,4-triazol-3-amine with the corresponding ortho esters in the presence of acetic acid. Imino esters **1a**–**1c** were selected as model substrates to react with cyanamide, carbon disulfide, and sodium thiocyanate with the goal of obtaining compounds **2**–**4** (Scheme 1, Table 1). Treatment of **1a**–**1c** with cyanamide in methanol under reflux gave triazolotriazinamines **2a**–**2c** whose IR, ^{1}H and ^{13}C NMR, and mass spectra and elemental analyses were in good agreement with the assigned structures (see Experimental). The IR spectra of **2** exhibited absorption bands at 3130–3200 (NH_2) and 1618 cm^{-1} (C=N). The ^{1}H NMR spectrum of **2c** showed signals of aromatic protons in the region δ 7.10–7.65 ppm. The presence of an amino group in molecules **2a**–**2c** was confirmed by the disappearance of signals at δ 7.32 (**2a**), 7.12 (**2b**), and 7.52 ppm (**2c**) after addition of D_2O. Furthermore, neither NH nor EtO signals typical of initial esters **1** were observed. The ^{13}C NMR spectra of **2** were also consistent with the proposed structure.

The reaction of **1** with carbon disulfide is likely to involve initial proton elimination from the N^{4}H group by pyridine. The second step is nucleophilic attack of the N^4 nitrogen atom of **1** on the C=S carbon atom. Finally, intramolecular cyclization affords triazolothiadiazinethione **3** (Scheme 1). The IR spectra of **3a**–**3c** showed absorption bands corresponding to C=N and C=S bonds at 1615 and 1250 cm^{-1}, whereas no N–H

Scheme 1.



R = Me (**a**), Et (**b**), Ph (**c**).

stretching band was present. In the ^{13}C NMR spectra of **3a**–**3c**, the C=S carbon atom resonated at δ_C 172.2 (**3a**), 173.5 (**3b**), and 171.1 ppm (**3c**) in addition to other characteristic carbon signals.

The reaction of **1a**–**1c** with an equimolar amount of sodium thiocyanate (NaSCN) in ethanol under reflux for 12 h afforded [1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazin-5-imines **4a**–**4c**. The IR spectra of **4** showed absorption bands in the regions 1628–1622 (C=N) and 3450–3440 cm^{-1} (=N–H). The ^{1}H NMR spectrum of **4c** displayed two multiplets in the region δ 7.3–7.8 ppm due to aromatic protons and a broadened singlet at δ 4.83 ppm due to =NH.

In conclusion, the proposed method seems to be economically feasible because the products can be obtained through a facile two-step reaction from commercially available and relatively inexpensive chemicals. Further research on biological activity of heterocyclic compounds **2a**–**2c**, **3a**–**3b**, and **4a**–**4c** is needed.

EXPERIMENTAL

The IR spectra were recorded with a Nicolet IR200 FT-IR spectrometer (USA). The ^{1}H and ^{13}C NMR spectra were recorded on a on a Bruker AC 300 spectrometer (USA; 300 MHz for ^{1}H) using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The melting points were determined on an Electrothermal 9100 melting point apparatus (Weiss-Gallenkamp, Loughborough, UK). Elemental micro analysis was performed on a Perkin Elmer 2400 Series II CHNS/O analyzer (USA). The mass spectra (positive electron spray ionization) were recorded on a Bruker Daltonics LC/MS instrument (USA). All chemicals, reagents, and solvents were obtained from Sigma–Aldrich and were used without any purification. The yields and melting points of compounds **1a**–**1c**, **2a**–**2c**, **3a**–**3b**, and **4a**–**4c** are given in Table 1.

***N*-(4*H*-1,2,4-Triazol-3-yl) carboximidates 1a–1c** were synthesized by heating 4*H*-1,2,4-triazol-3-amine with excess triethyl orthoacetate, triethyl orthopropionate, or triethyl orthobenzoate in the presence of

Table 1. Yields and melting points of compounds **1a**–**1c**, **2a**–**2c**, **3a**–**3c**, and **4a**–**4c**

Compound no.	Yield, %	mp, °C
1a	65	150–152
1b	68	162–164
1c	74	148–150
2a	66	280–282
2b	55	290–292
2c	75	275–277
3a	60	180–182
3b	65	195–197
3c	70	205–208
4a	48	230–233
4b	53	217–219
4c	67	286–288

acetic acid under reflux for 3 h. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ethanol.

Ethyl *N*-(4*H*-1,2,4-triazol-3-yl)acetimidate (1a). IR spectrum: ν 1660 cm^{-1} (C=N). ^1H NMR spectrum, δ, ppm: 1.42 t (3H, C**H**$_3$CH$_2$), 2.30 s (3H, CH$_3$C=N), 4.18 q (2H, CH$_2$O), 8.82 s (1H, 5-H), 10.80 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 16.4, 23.2, 62.2, 152.9, 154.1, 161.2. Found, %: C 46.85; H 6.68; N 36.40. $C_6H_{10}N_4O$. Calculated, %: C 46.74; H 6.54; N 36.34.

Ethyl *N*-(4*H*-1,2,4-triazol-3-yl)propanimidate (1b). IR spectrum, ν, cm^{-1}: 3425 (N–H), 1664 (C=N). ^1H NMR spectrum, δ, ppm: 1.12 t (3H, C**H**$_3$CH$_2$C), 1.52 q (2H, CH$_3$C**H**$_2$C), 1.44 t (3H, C**H**$_3$CH$_2$O), 4.20 q (2H, CH$_2$O), 8.75 s (1H, 5-H), 10.65 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 12.4, 16.1, 24.4, 61.6, 151.8, 155.5, 160.8. Found, %: C 50.12; H 7.23; N 33.38. $C_7H_{12}N_4O$. Calculated, %: C 49.99; H 7.19; N 33.31.

Ethyl *N*-(4*H*-1,2,4-triazol-3-yl)benzimidate (1c). IR spectrum, ν, cm^{-1}: 3422 (N–H), 1661 (C=N). ^1H NMR spectrum, δ, ppm: 1.42 t (3H, C**H**$_3$CH$_2$), 4.21 q (2H, CH$_2$O), 7.14–7.52 m (5H, H$_{arom}$), 9.63 s (1H, 5-H), 10.77 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 16.4, 62.4, 130.1, 129.2, 128.2 (2C), 127.6 (2C), 153.2, 156.5, 162.1. Found, %: C 61.07; H 5.47; N 25.93. $C_{11}H_{12}N_4O$. Calculated, %: C 61.10; H 5.59; N 25.91.

[1,2,4]Triazolo[4,3-*a*][1,3,5]triazin-5-amines 2a–2c (*general procedure*). A mixture of compound **1a–1c** (2 mmol) and cyanamide (2 mmol) in methanol (15 mL) was refluxed for 48 h. The solvent was removed under reduced pressure, and the solid product was filtered off and recrystallized from ethanol.

7-Methyl[1,2,4]triazolo[4,3-*a*][1,3,5]triazin-5-amine (2a). IR spectrum, ν, cm^{-1}: 3130–3200 (NH$_2$), 1618 (C=N). ^1H NMR spectrum, δ, ppm: 2.20 s (3H, CH$_3$), 8.72 s (1H, 3-H), 7.32 br.s (2H, NH$_2$, D$_2$O exchangeable). ^{13}C NMR spectrum, δ_C, ppm: 23.2, 151.7, 152.9, 154.1, 161.2. Mass spectrum: *m*/*z* 151 $[M + H]^+$. Found, %: C 40.05; H 4.08; N 55.99. $C_5H_6N_6$. Calculated, %: C 40.00; H 4.03; N 55.97.

7-Ethyl[1,2,4]triazolo[4,3-*a*][1,3,5]triazin-5-amine (2b). IR spectrum, ν, cm^{-1}: 3130–3200 (NH$_2$), 1618 (C=N). ^1H NMR spectrum, δ, ppm: 1.15 t (3H, *J* = 7.2 Hz, C**H**$_3$CH$_2$), 2.25 q (2H, *J* = 7.2 Hz, CH$_3$C**H**$_2$), 8.60 s (1H, 3-H), 7.12 br.s (2H, NH$_2$, D$_2$O exchangeable). ^{13}C NMR spectrum, δ_C, ppm: 10.8, 20.6, 150.1, 152.1, 153.8, 163.7. Mass spectrum: *m*/*z* 165 $[M + H]^+$. Found, %: C 43.97; H 4.95; N 51.23. $C_6H_8N_6$. Calculated, %: C 43.90; H 4.91; N 51.19.

7-Phenyl[1,2,4]triazolo[4,3-*a*][1,3,5]triazin-5-amine (2c). IR spectrum, ν, cm^{-1}: 3130–3200 (NH$_2$), 1618 (C=N). ^1H NMR spectrum, δ, ppm: 7.15–7.65 m (5H, H$_{arom}$), 9.12 s (1H, 3-H), 7.52 br.s (2H, NH$_2$, D$_2$O exchangeable). ^{13}C NMR spectrum, δ_C, ppm: 113.1, 115.3, 115.8, 126.3, 126.9, 131.7, 152.2, 154.1, 155.6, 162.4. Mass spectrum: *m*/*z* 213 $[M + H]^+$. Found, %: C 56.63; H 3.82; N 39.64. $C_{10}H_8N_6$. Calculated, %: C 56.60; H 3.80; N 39.60.

[1,2,4]Triazolo[4,3-*c*][1,3,5]thiadiazine-5-thiones 3a–3c (*general procedure*). A mixture of **1a–1c** (3 mmol) and carbon disulfide (3.2 mmol) in anhydrous ethanol (10 mL) containing pyridine (3.2 mmol) was refluxed for 24 h. After cooling, the solvent was evaporated under reduced pressure, and the resulting solid was collected by filtration, washed with ether, and recrystallized from methanol.

7-Methyl-5*H*-[1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazine-5-thione (3a). IR spectrum, ν, cm^{-1}: 1615 (C=N), 1250 (C=S). ^1H NMR spectrum, δ, ppm: 1.71 s (3H, CH$_3$), 10.01 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 19.3, 150.3, 152.1, 166.53, 172.2. Mass spectrum: *m*/*z* 185 $[M + H]^+$. Found, %: C 32.61; H 2.21; N 30.43. $C_5H_4N_4S_2$. Calculated, %: C 32.59; H 2.19; N 30.41.

7-Ethyl-5*H*-[1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazine-5-thione (3b). IR spectrum, ν, cm^{-1}: 1615 (C=N), 1250 (C=S). ^1H NMR spectrum, δ, ppm: 1.10 t (3H, *J* = 9.0 Hz, C**H**$_3$CH$_2$), 2.28 q (2H, *J* = 9.0 Hz, CH$_3$C**H**$_2$), 10.09 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 11.3, 18.20, 151.8, 152.5, 165.6, 173.5. Mass spectrum: *m*/*z* 199 $[M + H]^+$. Found, %: C 36.37; H 3.08; N 28.29. $C_6H_6N_4S_2$. Calculated, %: C 36.35; H 3.05; N 28.26.

7-Phenyl-5*H*-[1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazine-5-thione (3c). IR spectrum, ν, cm^{-1}: 1615 (C=N), 1250 (C=S). ^1H NMR spectrum, δ, ppm: 9.95 s (1H, 3-H), 7.11–7.91 m (5H, H$_{arom}$). ^{13}C NMR spectrum, δ_C, ppm: 112.6, 115.2, 115.8, 127.3, 127.5, 132.1, 151.2, 152.2, 164.9, 170.1. Mass spectrum: *m*/*z* 247 $[M + H]^+$. Found, %: C 48.79; H 2.48; N 22.77. $C_{10}H_6N_4S_2$. Calculated, %: C 48.76; H 2.46; N 22.75.

[1,2,4]Triazolo[4,3-*c*][1,3,5]thiadiazin-5-imines 4a–4c (*general procedure*). Equimolecular amounts (1 mmol) of compound **1a–1c** and sodium thiocyanate were dissolved under vigorous stirring in a mixture of

ethanol (17 mL) and water (3 mL). After complete dissolution of the reagents, the solution was refluxed for 12 h. After cooling to room temperature, the solution was extracted with methylene chloride (3×20 mL). The organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was recrystallized from methanol.

7-Methyl-5*H*-[1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazin-5-imine (4a). IR spectrum, ν, cm^{-1}: 3440 (N–H), 1628 (C=N). ^1H NMR spectrum, δ, ppm: 1.62 s (3H, CH_3), 4.85 br.s (1H, =NH), 9.25 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 16.8, 153.1, 166.1, 170.2. Mass spectrum: *m*/*z* 168 $[M + H]^+$. Found, %: C 35.97; H 3.08; N 41.93. $C_5H_5N_5S$. Calculated, %: C 35.92; H 3.01; N 41.89.

7-Ethyl-5*H*-[1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazin-5-imine (4b). IR spectrum, ν, cm^{-1}: 3446 (N–H), 1625 (C=N). ^1H NMR spectrum, δ, ppm: 1.03 t (3H, J = 8.4 Hz, $CH_2C\mathbf{H}_3$), 2.53 q (2H, J = 8.2 Hz, $C\mathbf{H}_2CH_3$), 4.85 br.s (1H, =NH), 9.91 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 11.8, 21.7, 154.2, 165.5, 170.9. Mass spectrum: *m*/*z* 182 $[M + H]^+$. Found, %: C 39.80; H 3.91; N 38.69. $C_6H_7N_5S$. Calculated, %: C 39.77; H 3.89; N 38.65.

7-Phenyl-5*H*-[1,2,4]triazolo[4,3-*c*][1,3,5]thiadiazin-5-imine (4c). IR spectrum, ν, cm^{-1}: 3450 (N–H), 1622 (C=N). ^1H NMR spectrum, δ, ppm: 7.32–7.80 m (5H, H_{arom}), 4.83 br.s (1H, =NH), 10.11 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 109.6, 112.2, 112.9, 125.1, 125.5, 129.6, 150.8, 164.8, 170.7. Mass spectrum: *m*/*z* 230 $[M + H]^+$. Found, %: C 52.43; H 3.09; N 30.57. $C_{10}H_7N_5S$. Calculated, %: C 52.39; H 3.08; N 30.55.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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