Synthesis of 1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]-1,3-thiazine derivatives

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2-R-5-Imino-6*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones react with aromatic and heterocyclic aldehydes in the presence of Et_3N to give condensation products on the methylene group, which react with carbon disulfide to yield the corresponding 2,6-disubstituted 8-thioxo-9,9a-dihydro-1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-ones.

Key words: 2-R-5-imino-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones, aromatic aldehydes, condensation, basic catalysis; 2-R-6-arylmethylene-5-imino-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones, carbon disulfide, cycloaddition; 8-thioxo-9,9a-dihydro-1,3,4-thiadiazolo[3′,2′:1,2]-pyrimidino[5,6-*d*]1,3-thiazin-5-ones.

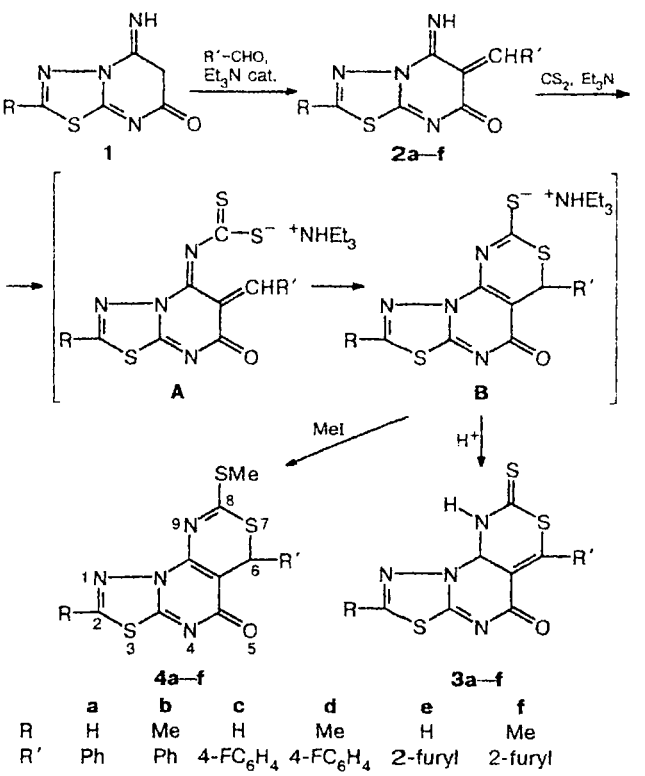
Literature data on fused heterocycles with a thiadiazolo[3,2-*a*]pyrimidine system annelated with another ring are scarce. These include 1,3,4-thiadiazolo[2,3-*b*]quinozalines,[1–3] pyrazolo[3,4-*e*]1,3,4-thiadiazolo[3,2-*a*]pyrimidines,[4] and 1,3,4-thiadiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidines.[5]

The catalyzed addition of thioamides, dithiocarbamates, and thiourea to ylidene compounds containing a ketone, amine, or imine fragment is a common method for the synthesis of 1,3-thiazine derivatives.[6–8]

It is known[6–8] that 2-arylidenecyclanes easily enter into acid-catalyzed reactions with dithiocarbamic acids, and the Michael addition of the thiol group to the ylidene fragment occurs with subsequent condensation of the amide group with the ketone fragment to give fused 1,3-thiazine derivatives.

The present paper describes the synthesis of derivatives of 1,3,4-thiadiazolo[3,2:1,2]pyrimidino[5,6-*d*]1,3-thiazine, a new tricyclic system, by the reaction of 2-R-5-imino-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones (**1**) (R = H or Me) with aromatic aldehydes followed by the cycloaddition of products of condensation with CS_2. Compound **1** was found to react smoothly with benzaldehyde, 4-fluorobenzaldehyde, and furfural on the methylene group of the pyrimidine ring in polar solvents such as ethanol, dioxane, THF, DMSO, or DMF in the presence of catalytic amounts of Et_3N at 20 °C to give the corresponding 2-R-6-arylmethylene-5-imino-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones (**2a—f**). The cycloaddition of the latter with CS_2 in the presence of Et_3N (1 equiv.) gives 2,6-disubstituted 8-thioxo-9,9a-dihydro-1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-ones (**3a—f**) (Scheme 1). These compounds may also be obtained in a one-pot procedure directly from **1**

Scheme 1



	a	b	c	d	e	f
R	H	Me	H	Me	H	Me
R′	Ph	Ph	4-FC_6H_4	4-FC_6H_4	2-furyl	2-furyl

without isolation of **2a—f**. Apparently, the reaction of **2a—f** with CS_2 proceeds *via* dithiocarbamates (**A**), which further undergo intramolecular cyclization to give triethylammonium salts **3a—f** (**B**).

The triethylammonium salts **B** are *S*-methylated without isolation with MeI to give 8-methylthio-1,3,4-

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thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-ones (**4a—f**).

The structures of compounds **2—4** were confirmed by data from ^{1}H NMR and IR spectroscopy and elemental analysis. The IR spectra of the compounds exhibit absorption bands at 3170—3140 and 1685—1660 cm^{-1} corresponding to the N—H and C=O stretching vibrations. In the ^{1}H NMR spectra of compounds **2a—f**, the CH=C proton manifests itself as a singlet at δ 8.40—8.07. The chemical shifts for the CH proton of the thiadiazole ring in compounds **2a,c,e**, **3a,c,e**, and **4a,c,e** are at δ 9.06—8.04. In addition, a singlet for the thiazine ring appear at δ 8.40—8.14.

Experimental

IR spectra were recorded on a UR-20 instrument (thin film). ^{1}H NMR spectra were recorded on a Tesla BS-587C instrument (100 MHz) in DMSO-d_6 with HMDS as the internal standard. The melting points of crystalline compounds were measured with a Boetius instrument on glass plates. Compounds **1** (R = H or Me) were synthesized according to the known procedures.[9,10]

Synthesis of compounds 2a—f, 3a—f, and 4a—f (general procedure). Aldehyde (0.0105 mol) and three drops of Et_3N were added to a solution of thiadiazolopyrimidine **1** (0.01 mol) in 10 mL of DMF and 10 mL of ethanol The reaction mixture was heated at 50—60 °C for 2—3 h until crystallization began and left for 10—12 h. Then the precipitate was filtered off and washed with dry ether to give condensation products **2a—f**. Compounds **3a—f** were synthesized under the same conditions by the reaction of thiadiazolopyrimidine **1**, aldehyde, Et_3N (0.01 mol), and CS_2 (0.011 mol). Heterocycles **3a—f** were isolated by acidification with AcOH and dilution with water (50—60 mL). Compounds **4a—f** were synthesized under the same conditions. A mixture of compound **1**, aldehyde, Et_3N (0.01 mol), CS_2 (0.011 mol), and MeI (0.01 mol) was stirred for 2—3 h to give a precipitate. The reaction mixture was diluted with water (100 mL), and the precipitate that formed was filtered off, washed with water (3×20 mL), and dried in air. Compounds **2a—f**, **3a—f**, and **4a—f** were recrystallized from aqueous dioxane.

6-Benzylidene-5-imino-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (2a). Yield 78.0%, m.p. 250—253 °C. Found (%): N, 21.57. $C_{12}H_8N_4OS$. Calculated (%): N, 21.86. IR, ν/cm^{-1}: 3140, 3100, 2950, 2230, 1670, 1610, 1560, 1460, 1335, 1230, 900, 835, 765, 685. ^{1}H NMR, δ: 7.58—7.96 (m, 5 H, Ph); 8.25 (s, 1 H, CH=C); 8.86 (s, H(2)).

6-Benzylidene-5-imino-2-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (2b). Yield 81.5%, m.p. 240—243 °C. Found (%): N, 20.86. $C_{13}H_{10}N_4OS$. Calculated (%): N, 20.73. IR, ν/cm^{-1}: 3155, 3050, 2230, 1665, 1615, 1560, 1450, 1325, 1260, 1220, 900, 832, 755, 690. ^{1}H NMR, δ: 2.46 (s, 3 H, Me); 7.48—7.96 (m, 5 H, Ph); 8.35 (s, 1 H, CH=C).

6-(4-Fluorobenzylidene)-5-imino-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (2c). Yield 76.5%, m.p. 282—285 °C. Found (%): N, 20.11. $C_{12}H_7FN_4OS$. Calculated (%): N, 20.43. IR, ν/cm^{-1}: 3090, 2970, 2235, 1685, 1605, 1560, 1425, 1335, 1255, 1170, 900, 840, 740, 540, 510. ^{1}H NMR, δ: 7.26—8.10 (m, 4 H, Ph); 8.42 (s, 1 H, CH=C); 9.06 (s, 1 H, H(2)).

6-(4-Fluorobenzylidene)-5-imino-2-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (2d). Yield 87.0%, m.p. 250—252 °C. Found (%): N, 19.16. $C_{13}H_9FN_4OS$. Calculated (%): N, 19.43. IR, ν/cm^{-1}: 3170, 3070, 2950, 2235, 1670, 1605, 1560, 1430, 1330, 1260, 1175, 905, 845, 540, 510. ^{1}H NMR, δ: 2.48 (s, 3 H, Me); 7.22—8.08 (m, 4 H, Ph); 8.34 (s, CH=C).

6-Furfurylidene-5-imino-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (2e). Yield 81.0%, m.p. 280—283 °C. Found (%): N, 22.43. $C_{10}H_6N_4O_2S$. Calculated (%): N, 22.75. IR, ν/cm^{-1}: 3165, 3050, 2230, 1670, 1630, 1560, 1405, 1320, 1270, 1210, 1025, 885, 780, 740, 595. ^{1}H NMR, δ: 6.74 (q, 1 H, 4′-H furyl); 7.36 (d, 1 H, 3′-H furyl); 8.05 (d, 1 H, 5′-H furyl); 8.17 (s, 1 H, CH=C); 9.00 (s, 1 H, H(2)).

6-Furfurylidene-5-imino-2-methyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (2f). Yield 92.3%, m.p. 270—273 °C. Found (%): N, 21.38. $C_{11}H_8N_4O_2S$. Calculated (%): N, 21.53. IR, ν/cm^{-1}: 3160, 3045, 2235, 1660, 1630, 1565, 1405, 1325, 1265, 1220, 1025, 890, 850, 770, 720, 597. ^{1}H NMR, δ: 2.44 (s, 3 H, Me); 6.75 (q, 1 H, 4′-H furyl); 7.38 (d, 1 H, 3′-H furyl); 8.07 (d, 1 H, 5′-H furyl); 8.24 (s, CH=C).

6-Phenyl-8-thioxo-9,9a-dihydro-1,3,4-thiadiazolo-[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (3a). Yield 63.0%, m.p. 275—277 °C. Found (%): N, 16.71. $C_{13}H_8N_4OS_3$. Calculated (%): N, 16.85. IR, ν/cm^{-1}: 3284, 3064, 2704, 2540, 1785, 1674, 1660, 1644, 1590, 1456, 1364, 1276, 988, 906, 872. ^{1}H NMR, δ: 7.65—8.02 (m, 5 H, Ph); 8.45 (s, 1 H, NH); 9.08 (s, 1 H, H(2)).

2-Methyl-6-phenyl-8-thioxo-9,9a-dihydro-1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (3b). Yield 72.0%, m.p. 244—246 °C. Found (%): N, 16.01. $C_{14}H_{10}N_4OS_3$. Calculated (%): N, 16.17. IR, ν/cm^{-1}: 3140, 3040, 2228, 1668, 1622, 1566, 1504, 1462, 1137, 1238, 1010, 856, 734, 696. ^{1}H NMR, δ: 2.50 (s, 3 H, Me); 7.53—7.81 (m, 5 H, Ph); 8.41 (s, 1 H, NH).

6-(4-Fluorophenyl)-8-thioxo-9,9a-dihydro-1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (3c). Yield 60.0%, m.p. 272—274 °C. Found (%): N, 16.10. $C_{13}H_7FN_4OS_3$. Calculated (%): N, 15.99. IR, ν/cm^{-1}: 3088, 2288, 2228, 1674, 1660, 1572, 1510, 1360, 1276, 1164, 984, 896, 750, 586, 544. ^{1}H NMR, δ: 7.33—8.00 (m, 4 H, Ph); 8.46 (s, 1 H, NH); 9.16 (s, 1 H, H(2)).

6-(4-Fluorophenyl)-2-methyl-8-thioxo-9,9a-dihydro-1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (3d). Yield 71.0%, m.p. 262—264 °C. Found (%): N, 15.44. $C_{14}H_9FN_4OS_3$. Calculated (%): N, 15.37. IR, ν/cm^{-1}: 3484, 3088, 3047, 2376, 1672, 1660, 1574, 1458, 1360, 1270, 1178, 1036, 912, 900, 862. ^{1}H NMR, δ: 2.52 (s, 3 H, Me); 7.32—8.07 (m, 4 H, Ph); 8.23 (s, 1 H, NH).

6-(2-Furyl)-8-thioxo-9,9a-dihydro-1,3,4-thiadiazolo-[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (3e). Yield 63.0%, m.p. 274—276 °C. Found (%): N, 17.45. $C_{11}H_6N_4O_2S_3$. Calculated (%): N, 17.38. IR, ν/cm^{-1}: 3292, 3088, 2264, 1672, 1668, 1600, 1584, 1432, 1278, 1222, 1152, 1148, 1110, 968, 630. ^{1}H NMR, δ: 6.77 (q, 1 H, 4′-H furyl); 7.36 (d, 1 H, 3′-H furyl); 8.09 (d, 1 H, 5′-H furyl); 8.21 (s, 1 H, NH); 9.10 (s, 1 H, H(2)).

6-(2-Furyl)-2-methyl-8-thioxo-9,9a-dihydro-1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (3f). Yield 62.0%, m.p. 262—264 °C. Found (%): N, 16.71. $C_{12}H_8N_4O_2S_3$. Calculated (%): N, 16.65. IR, ν/cm^{-1}: 3336, 3080, 2324, 1806, 1674, 1668, 1534, 1580, 1478, 1280, 1226, 1164, 998, 900, 852, 746. ^{1}H NMR, δ: 2.40 (s, 3 H, Me); 6.76 (q, 1 H, 4′-H furyl); 7.40 (d, 1 H, 3′-H furyl); 8.11 (d, 1 H, 5′-H furyl); 8.27 (s, NH).

8-Methylthio-6-phenyl-1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (4a). Yield 66.4%, m.p. 180—182 °C. Found (%): C, 48.03; H, 2.70. $C_{14}H_{10}N_4OS_3$. Calcu-

lated (%): C, 48.53; H, 2.88. IR, ν/cm^{-1}: 1650 (C=O); 1642 (C=N); 1624 (C=N). ^1H NMR, δ: 8.94 (s, 1 H, H(2)); 8.44 (s, 1 H, H(6)); 7.98—7.52 (m, 5 H, Ph); 3.90 (s, 3 H, Me).

2-Methyl-8-methylthio-6-phenyl-1,3,4-thiadiazolo-[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (4b). Yield 70.0%, m.p. 150—152 °C. Found (%): C, 42.63; H, 2.31. $C_{15}H_{12}N_4OS_3$. Calculated (%): C, 42.84; H, 2.40. IR, ν/cm^{-1}: 1678 (C=O); 1654 (C=N); 1624 (C=N). ^1H NMR, δ: 8.40 (s, 1 H, H(6)); 8.00—7.46 (m, 5 H, Ph); 3.84 (s, 3 H, MeS); 2.44 (s, 3 H, Me).

6-(4-Fluorophenyl)-8-methylthio-1,3,4-thiadiazolo-[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (4c). Yield 92.8%, m.p. 185—186 °C. Found (%): C, 46.29; H, 2.31. $C_{14}H_9FN_4OS_3$. Calculated (%): C, 46.14; H, 2.49. IR, ν/cm^{-1}: 1660 (C=O); 1644 (C=N); 1628 (C=N). ^1H NMR, δ: 8.94 (s, 1 H, H(2)); 8.44 (s, 1 H, H(6)); 8.08 (d, 2 H, Ph); 7.32 (d, 2 H, Ph); 3.80 (s, 3 H, Me).

6-(4-Fluorophenyl)-2-methyl-8-methylthio-1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (4d). Yield 84.6%, m.p. 212—214 °C. Found (%): C, 47.17; H, 2.39. $C_{15}H_{11}FN_4OS_3$. Calculated (%): C, 47.60; H, 2.93. IR, ν/cm^{-1}: 1680 (C=O); 1656 (C=N); 1628 (C=N). ^1H NMR, δ: 8.40 (s, 1 H, H(6)); 8.00 (d, 2 H, Ph); 7.32 (d, 2 H, Ph); 3.82 (s, 3 H, MeS); 2.22 (s, 3 H, Me).

6-(2-Furyl)-8-methylthio-1,3,4-thiadiazolo[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (4e). Yield 86.9%, m.p. 204—206 °C. Found (%): C, 42.40; H, 2.21. $C_{12}H_8N_4O_2S_3$. Calculated (%): C, 42.84; H, 2.40. IR, ν/cm^{-1}: 1662 (C=O); 1648 (C=N); 1640 (C=N). ^1H NMR, δ: 8.92 (s, 1 H, H(2)); 8.18 (s, 1 H, H-6); 8.06 (d, 1 H, 5′-H furyl); 7.38 (d, 1 H, 3′-H furyl); 6.76 (q, 1 H, 4′-H furyl); 3.88 (s, 1 H, Me).

6-(2-Furyl)-2-methyl-8-methylthio-1,3,4-thiadiazolo-[3′,2′:1,2]pyrimidino[5,6-*d*]1,3-thiazin-5-one (4f). Yield 88.5%, m.p. 200—202 °C. Found (%): C, 44.31; H, 2.59. $C_{13}H_{10}N_4O_2S_3$. Calculated (%): C, 44.55; H, 2.40. IR, ν/cm^{-1}: 1669 (C=O); 1650 (C=N); 1638 (C=N). ^1H NMR, δ: 8.14 (s, 1 H, H(6)); 8.04 (d, 1 H, 5′-H furyl); 7.36 (d, 1 H, 3′-H furyl); 6.74 (q, 1 H, 4′-H furyl); 3.88 (s, 3 H, MeS); 2.40 (s, 3 H, Me).

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