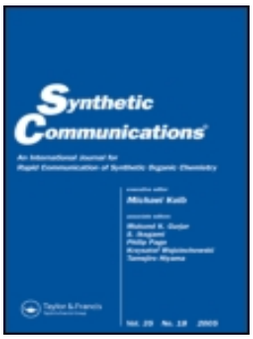

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ONE-POT SYNTHESIS OF 1,3,4-THIADIAZIN-5-YL-CHROMEN-2-ONE DERIVATIVES VIA THREE-COMPONENT REACTION

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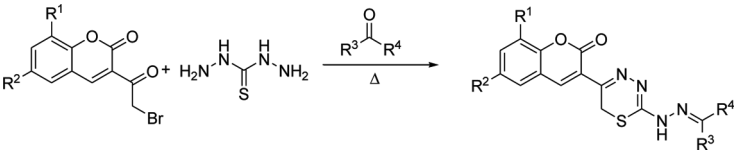
GRAPHICAL ABSTRACT



Abstract *An expeditious, one-pot reaction has been described for the preparation of 1,3,4-thiadiazin-5-yl-chromen-2-one derivatives. These compounds were synthesized by the reaction of 3-(2-bromoacetyl)coumarin with thiocarbohydrazide and various carbonyl compounds. The newly synthesized compounds were characterized by infrared, ^1H NMR, and mass spectra.*

Keywords 3-(2-Bromoacetyl)coumarin; one-pot synthesis; 1,3,4-thiadiazine; thiocarbohydrazide

INTRODUCTION

1,3,4-Thiadiazines constitute an important class of heterocycles, which has attracted much synthetic interest because of their wide range of biological activities. Considerable attention has been focused on these compounds because many of these derivatives are important matrix metalloproteinase inhibitors.[1] They show excellent cardiotonic and hypertensive activities.[2,3] They act as phosphodiesterase(IV) inhibitors. These can be used for treatment of tumors and acquired immune deficiency syndrome (AIDS).[4] The literature survey reveals that there are not many examples of 1,3,4-thiadiazines. These can be prepared by the reaction of thiosemicarbazide or thiocarbohydrazide with α-halo ketones.[5] Some heteroaryl-1,3,4-thiadiazines have been reported in the literature starting from phenacyl bromide or chloroacetic acid and pyrazolyl-1-thiocarbonylhydrazide.[6]

Benzopyran-2-one (coumarin) and its derivatives have also found various medicinal applications such as antitumoral, anti-inflammatory, antiviral, central nevous

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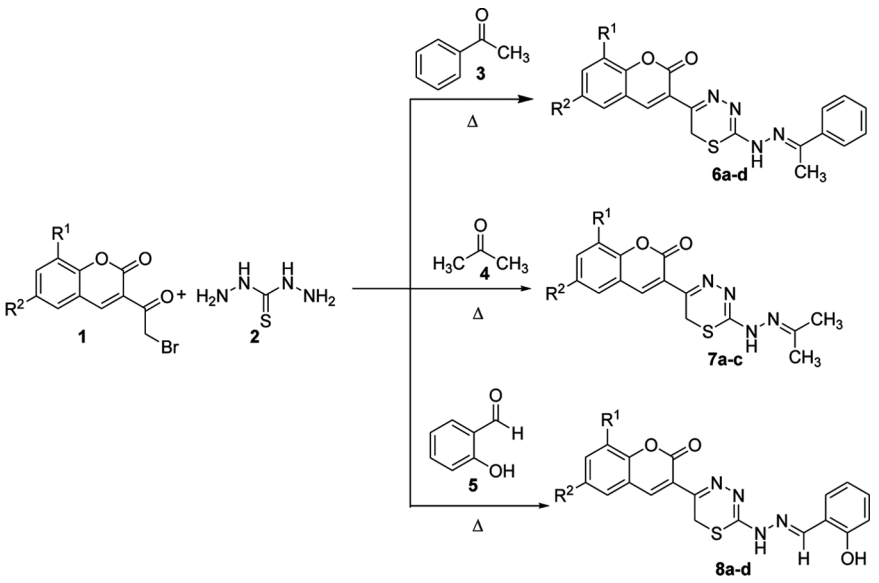


Scheme 1. Synthesis of 1,3,4-thiadiazin-5-yl-chromen-2-one derivatives via one-pot, three-component reaction. **6a:** $R^1 = H$, $R^2 = OMe$; **6b:** $R^2 = H$, $R^1 = H$; **6c**: $R^1 = Br$, $R^2 = Br$; **6d**: 5,6-benzo analog of **6a**. **7a**: $R^1 = H$, $R^2 = H$; **7b**: $R^1 = Br$, $R^2 = Br$; **7c**: 5,6-benzo analog of **7a**. **8a**: $R^1 = H$, $R^2 = H$; **8b**: $R^1 = H$, $R^2 = Br$; **8c**: $R^1 = Br$, $R^2 = Br$; **8d**: 5,6-benzo analog of **8a**.

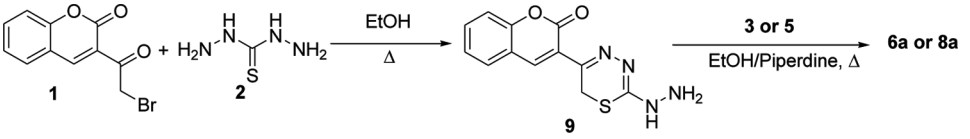
system, and antioxidant activities.[7–9] These derivatives have been found to be novel lipid-lowering agents that possess moderate triglyceride-lowering activity.[10] Some of the coumarin derivatives are known for their anti-HIV activities.[11–14]

In view of various biological activities of 1,3,4-thiadiazines and in continuation of our earlier work on the synthesis of new heterocyclic compounds[15–18] with anticipated biological activities, we have investigated a practical approach for the synthesis of heterocyclic compounds like 1,3,4-thiadiazines at the third position of 2H-benzopyran-2-one via a one-pot, three-component reaction under mild and efficient conditions.

RESULTS AND DISCUSSION

Condensation of various 3-(2-bromoacetyl)coumarins with thiocarbohydrazide in 1.5–2 mL of acetone or acetophenone or salicylaldehyde gave the title products in excellent yields. To reduce the side products, we have stirred the reaction mixture at room temperature for about 30 min, followed by stirring at 50–55 °C for about 1 h to give the final products. The reaction path for the formation of products can be explained by the S-acylation of thiocarbohydrazide with **1**, followed by intramolecular cyclization to give coumarin substituted 2-hydrazino-6H-1,3,4-thiadiazines. These underwent further condensation with carbonyl function of the solvent to give the corresponding hydrazones **6**, **7**, and **8**.

All the structures of newly synthesized compounds were confirmed by their spectral data. The ^{1}H NMR spectrum of compound **6a** shows prominent peaks



Scheme 2. Two-step synthesis of 1,3,4-thiadiazin-5-yl-chromen-2-one derivatives.

for -CH_3 at δ 2.39, -CH_2 of thiadiazine at δ 3.87, and C-4 proton of coumarin at δ 8.31. Similarly, ^{1}H NMR spectrum of compound **8a** shows prominent peaks at δ 3.98 for -CH_2 of thiadiazine and C-4 proton of coumarin at δ 8.57. The ^{13}CNMR spectrum of **6a** also shows the peaks at δ 14.5, 23.6, and 161.4 for methyl, CH_2 of thiadiazine, and C=O of coumarin respectively. All the spectral data support the formation of title products.

The structures of final products were also confirmed by synthesizing **6a** and **8a** unambiguously. Reaction of equimolar mixture of 3-(2-bromoacetyl)coumarin, thiocarbohydrazide in ethanol, and a catalytic amount of acetic acid gave 3-(2-hydrazino-6*H*-[1,3,4]thiadiazin-5-yl)-chromen-2-one **9**. On reaction with **3** or **5** in ethanol and a catalytic amount of piperidine, this gave the corresponding hydrazone **6a** or **8a**. The products obtained by both methods were found to be identical by mixed melting-point measurements, thin-layer chromatography (TLC), and spectral data.

CONCLUSION

In conclusion, we have developed an efficient, practical, one-pot synthesis for the title compounds without application of any catalyst. This is a simple, mild, inexpensive, and environmentally benign reaction. The biological activity of these compounds is in progress.

EXPERIMENTAL

All the reagents and solvents were purchased from commercial sources and were used without any further purification unless otherwise stated. 3-(2-Bromoacetyl)coumarins[19] were prepared by literature procedure. Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India) and were uncorrected. CHNS analysis was done with a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E. Merck Mumbai, India). Infrared (IR) spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using tetramethylsilane as standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV.

General Procedure for the Synthesis of Compounds 6a–d, 7a–c, and 8a–d

3-(2-Bromoacetyl)coumarin (1 mmol), thiocarbohydrazide (1 mmol), and 1.5 mL of **3**, **4**, or **5** were taken in a conical flask and stirred at room temperature

for about 30 min. Then the reaction mixture was heated for about 1 h at 50–55 °C and cooled to room temperature; the solid separated was filtered, washed with cooled methanol, and recrystallized from a suitable solvent.

Data

3-{2-[N^{1}-(1-Phenyl-ethylidene)-hydrazino]-6*H*-[1,3,4]thiadiazin-5-yl}-chromen-2-one (6a). Recrystallization: ($CHCl_3$ + MeOH); color: yellow solid; yield 72%; mp 178–180 °C; IR (KBr, υ_{max}, cm^{-1}): 1602 (C=N), 1732 (C=O), 3105 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H, -CH_3), 3.87 (s, 2H, -CH_2 of thiadiazine), 7.41–7.48 (m, 5H, ArH), 7.67 (t, 1H, J = 7.6 Hz, ArH), 7.87 (m, 3H, 7.6 Hz, ArH), 8.31 (s, 1H, C-4 of coumarin), 11.71 (s, 1H, -NH, D_2O, exchangeable); ^{13}C NMR ($CDCl_3$ δ ppm): 14.5, 23.6, 116.1, 118.8, 123.5, 125.0, 126.2, 128.4, 129.4, 129.4, 132.8, 138.2, 141.5, 144.6, 153.5, 157.5, 159.3, 161.4; EI-MS 377 $[M + H]^+$. Anal. calcd. for $C_{20}H_{16}N_4O_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 63.76; H, 4.21; N, 14.83%.

8-Methoxy-3-{2-[N^{1}-(1-phenyl-ethylidene)-hydrazino]-6*H*-[1,3,4]thiadiazin-5-yl}-chromen-2-one (6b). Recrystallization: ($CHCl_3$ + MeOH); color: yellow solid; yield 75%; mp 184–186 °C; IR (KBr, υ_{max}, cm^{-1}): 1607 (C=N), 1714 (C=O), 3105 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46 (s, 3H, -CH_3), 3.92 (s, 2H, -CH_2 of thiadiazine), 3.94 (s, 3H, OMe), 7.35–7.44 (m, 6H, ArH), 7.85 (d, 2H, J = 7.6 Hz, ArH), 8.36 (s, 1H, C-4 of coumarin), 11.55 (s, 1H, -NH, D_2O, exchangeable). Anal. calcd. for $C_{21}H_{18}N_4O_3S$: C, 62.05; H, 4.46; N, 13.78. Found: C, 62.01; H, 4.40; N, 13.82%.

6,8-Dibromo-3-{2-[N^{1}-(1-phenyl-ethylidene)-hydrazino]-6*H*-[1,3,4]thiadiazin-5-yl}-chromen-2-one (6c). Recrystallization: ($CHCl_3$ + MeOH); color: yellow solid; yield 75%; mp 172–174 °C; IR (KBr, υ_{max}, cm^{-1}): 1602 (C=N), 1732 (C=O), 3103 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H, -CH_3), 3.86 (s, 2H, -CH_2 of thiadiazine), 7.75–7.95 (m, 5H, ArH), 8.12–8.23 (m, 2H, ArH), 8.26 (s, 1H, C-4 of coumarin), 11.75 (s, 1H, -NH, D_2O, exchangeable). Anal. calcd. for $C_{20}H_{14}Br_2N_4O_2S$: C, 44.97; H, 2.64; N, 10.49. Found: C, 44.93; H, 2.61; N, 10.42%.

3-{2-[N^{1}-(1-Phenyl-ethylidene)-hydrazino]-6*H*-[1,3,4]thiadiazin-5-yl}-benzo[*f*]chromen-3-one (6d). Recrystallization: ($CHCl_3$ + MeOH); color: yellow solid; yield 71%; mp 194–196 °C; IR (KBr, υ_{max}, cm^{-1}): 1585 (C=N), 1716 (C=O), 3159 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H, -CH_3), 3.93 (s, 2H, -CH_2 of thiadiazine), 7.41–7.43 (m, 3H, ArH), 7.65 (t, 2H, J = 6.8 Hz, ArH), 7.75–7.86 (m, 3H, ArH), 8.09 (d, 1H, J = 8.0 Hz), 8.26 (d, 1H, J = 8.0 Hz), 8.65 (s, 1H, C-4 of coumarin), 9.01 (s, 1H, ArH), 11.75 (s, 1H, -NH, D_2O, exchangeable). Anal. calcd. for $C_{24}H_{18}N_4O_2S$: C, 67.59; H, 4.25; N, 13.14. Found: C, 67.52; H, 4.21; N, 13.10%.

3-[2-(N^{1}-Isopropylidene-hydrazino)-6*H*-[1,3,4]thiadiazin-5-yl]-chromen-2-one (7a). Recrystallization: ($CHCl_3$ + MeOH); color: yellow solid; yield 70%; mp 172–174 °C; IR (KBr, υ_{max}, cm^{-1}): 1572 (C=N), 1718 (C=O), 3138 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 [s, 6H, -$(CH_3)_2$], 3.86 (s, 2H, -CH_2 of thiadiazine), 7.70–7.83 (m, 4H, ArH), 8.55 (s, 1H, C-4 of coumarin), 9.08 (s, 1H, -NH, D_2O,

exchangeable); EI-MS 315 $[M+H]^+$. Anal. calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82. Found: C, 57.27; H, 4.45; N, 17.77%.

6,8-Dibromo-3-[2-(N^1-isopropylidene-hydrazino)-6*H*-[1,3,4]thiadiazin-5-yl]-chromen-2-one (7b). Recrystallization: ($CHCl_3$ + MeOH); color: yellow solid; yield 77%; mp 160–162 °C; IR (KBr, υ_{max}, cm^{-1}): 1572 (C=N), 1723 (C=O), 3154 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 [s, 6H, -$(CH_3)_2$], 3.81 (s, 2H, -CH_2 of thiadiazine), 8.19 (d, 1H, $J = 2.4$ Hz, ArH), 8.22 (d, 1H, $J = 2.4$ Hz, ArH), 8.69 (s, 1H, C-4 of coumarin), 9.08 (s, 1H, -NH, D_2O, exchangeable). Anal. calcd. for $C_{15}H_{12}Br_2N_4O_2S$: C, 38.16; H, 2.56; N, 11.87. Found: C, 38.11; H, 2.51; N, 11.82%.

3-[2-(N^1-Isopropylidene-hydrazino)-6*H*-[1,3,4]thiadiazin-5-yl]-benzo[f]chromen-3-one (7c). Recrystallization: ($CHCl_3$ + MeOH); color: yellow solid; yield 75%; mp 194–194 °C; IR (KBr, υ_{max}, cm^{-1}): 1570 (C=N), 1720 (C=O), 3157 (NH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.67 (s, 6H, -$(CH_3)_2$), 3.82 (s, 2H, -CH_2 of thiadiazine), 8.11–8.30 (m, 4H, ArH), 8.52–8.54 (m, 2H, ArH), 8.60 (s, 1H, C-4 of coumarin), 9.13 (s, 1H, -NH, D_2O, exchangeable). Anal. calcd. for $C_{19}H_{16}N_4O_2S$: C, 62.62; H, 4.43; N, 15.37. Found: C, 62.57; H, 4.40; N, 15.31%.

3-{2-[N^1-(2-Hydroxy-benzylidene)-hydrazino]-6*H*-[1,3,4]thiadiazin-5-yl}-chromen-2-one (8a). Recrystallization: (MeOH + AcOH); color: yellow solid; yield 80%; mp 200–202 °C; IR (KBr, υ_{max}, cm^{-1}): 1602 (C=N), 1725 (C=O), 3152 (NH), 3427 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.98 (s, 2H, -CH_2 of thiadiazine), 7.35–7.56 (m, 4H, ArH), 7.68 (d, 2H, $J = 8.8$ Hz, ArH), 7.86 (d, 2H, $J = 7.6$ Hz, ArH), 8.35 (s, 1H, N=C-H), 8.57 (s, 1H, C-4 of coumarin), 10.25 (s, 1H, -NH, D_2O, exchangeable), 11.32 (s, 1H, -OH, D_2O, exchangeable). EI-MS 379 $[M+H]^+$. Anal. calcd. for $C_{19}H_{14}N_4O_3S$: C, 60.31; H, 3.73; N, 14.81. Found: C, 60.28; H, 3.70; N, 14.76%.

6-Bromo-3-{2-[N^1-(2-hydroxy-benzylidene)-hydrazino]-6*H*-[1,3,4]thiadiazin-5-yl}-chromen-2-one (8b). Recrystallization: (MeOH + AcOH); color: yellow solid; yield 76%; mp 190–192 °C; IR (KBr, υ_{max}, cm^{-1}): 1608 (C=N), 1734 (C=O), 3209 (NH), 3345 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.08 (s, 2H, -CH_2 of thiadiazine), 7.40–7.58 (m, 6H, ArH), 7.70 (s, 1H, ArH), 7.90 (s, 1H, -N=C-H), 8.50 (s, 1H, C-4 of coumarin), 10.32 (s, 1H, -NH, D_2O, exchangeable). Anal. calcd. for $C_{19}H_{13}BrN_4O_3S$: C, 49.90; H, 2.87; N, 12.25. Found: C, 49.86; H, 2.81; N, 12.20%.

6,8-Dibromo-3-{2-[N^1-(2-hydroxy-benzylidene)-hydrazino]-6*H*-[1,3,4]-thiadiazin-5-yl}-chromen-2-one (8c). Recrystallization: (MeOH + AcOH); color: yellow solid; yield 79%; mp 164–166 °C; IR (KBr, υ_{max}, cm^{-1}): 1602 (C=N), 1716 (C=O), 3195 (NH), 3395 (OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.14 (s, 2H, -CH_2 of thiadiazine), 7.31–7.39 (m, 2H, ArH), 7.72–7.86 (m, 3H, ArH), 8.12 (s, 1H, ArH), 8.34 (s, 1H, -N=C-H), 8.68 (s, 1H, C-4 of coumarin), 10.23 (s, 1H, -NH, D_2O, exchangeable), 10.79 (s, 1H, -OH, D_2O, exchangeable). Anal. calcd. for $C_{19}H_{12}Br_2N_4O_3S$: C, 42.56; H, 2.26; N, 10.45. Found: C, 42.51; H, 2.21; N, 10.41%.

3-{2-[N^1-(2-Hydroxy-benzylidene)-hydrazino]-6*H*-[1,3,4]thiadiazin-5-yl}-benzo[*f*]chromen-3-one (8d). Recrystallization: (MeOH + AcOH); color: yellow

solid; yield 76%; mp 188–190 °C; IR (KBr, υ_{max}, cm^{-1}): 1602 (C=N), 1732 (C=O), 3143 (NH), 3383 (OH); ^1H NMR (400 MHz, DMSO-d_6): δ 4.05 (s, 2H, -CH_2 of thiadiazine), 7.62–7.90 (m, 7H, ArH), 8.10 (s, 1H, -N=C-H), 8.24 (d, 1H, $J = 9.2$ Hz, ArH), 8.48–8.60 (m, 2H, ArH), 8.75 (s, 1H, C-4 of coumarin), 10.45 (s, 1H, -NH, D_2O, exchangeable), 11.46 (s, 1H, -OH, D_2O, exchangeable). Anal. calcd. for $C_{23}H_{16}N_4O_3S$: C, 64.47; H, 3.76; N, 13.08. Found: C, 64.42; H, 3.71; N, 12.97%.

General Procedure for the Synthesis of 3-(2-Hydrazino-6*H*-[1,3,4]-thiadiazin-5-yl)-chromen-2-one (9)

3-(2-Bromoacetyl)coumarin (1 mmol), thiocarbohydrazide (1 mmol) are taken in 5 mL of anhydrous ethanol, refluxed for about 1 h. The yellow solid obtained on cooling was filtered, washed with methanol, and recrystallized.

Recrystallization: ($CHCl_3$ + MeOH); yellow solid; yield 70%; mp 139–141 °C; IR (KBr, υ_{max}, cm^{-1}): 1607 (C=N), 1709 (C=O), 3316 (NH), 3466 (NH_2); ^1H NMR (400 MHz, DMSO-d_6): δ 4.01 (s, 2H, -CH_2 of thiadiazine), 7.34–7.50 (m, 2H, ArH), 7.70 (m, 1H, ArH), 7.89 (d, 1H, $J = 7.2$ Hz, ArH), 8.37 (s, 1H, C-4 of coumarin), 10.01 (s, 1H, -NH, D_2O, exchangeable), 12.0 (s, 2H, -NH_2, D_2O, exchangeable); EI-MS 275 [M + H]. Anal. calcd. for $C_{12}H_{10}N_4O_2S$: C, 52.54; H, 3.67; N, 20.43. Found: C, 52.50; H, 3.62; N, 20.49%.

General Procedure for the Synthesis of Compounds 6a and 8a from 3-(2-Hydrazino-6*H*-[1,3,4]thiadiazin-5-yl)-chromen-2-one 9

A mixture of compound **9** (1 mmol), **3** or **5** (1.2 mmol) in 5 mL of anhydrous ethanol, and one or two drops of piperidine was refluxed for about 1 h. The solid obtained was cooled, filtered, washed with methanol, and recrystallized.

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