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One pot synthesis of 1,3,4-thiadiazole thiazolidinone derivatives

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One pot synthesis of 2-(substitutedphenyl)-3-[5-(substitutedphenyl)-1,3,4-thiadiazol-2-yl]thiazolidin-4-one was developed by the reaction of 1,3,4-thiadiazole, substituted benzaldehyde and mercaptoacetic acid. These compounds were identified by IR, ^{1}H NMR, elemental analyses and 2-(4-methoxyphenyl)-3-[5-(3-methylphenyl)-1,3,4-thiadiazol-2-yl]thiazolidin-4-one was confirmed by single-crystal X-ray diffraction.

Keywords: thiazolidin-4-one, 1,3,4-thiadiazole, one pot synthesis, crystal structure

Among various biological heterocyclic compounds, the 1,3,4-thiadiazole derivatives have attracted specific interest due to their promising biological activity. For example, some 1,3,4-thiadiazole derivatives have been reported to possess anti-inflammatory, antiproliferative, antibacterial and fungicidal activities.[1-5]

Thiazolidinones are of considerable importance as pharmacophoric groups due to their well known biological activities including bactericidal, pesticidal, anticonvulsant, anti-inflammatory and antithyroidal activities.[6] For instance, some 2,3-diaryl-1,3-thiazolidin-4-ones have been reported to show strong and selective anti-HIV activities.[7-11] Therefore, studies of the synthesis and pharmacology of thiazolidinone derivatives have attracted more interest in recent years.[12]

In connection with our research programme directed toward the synthesis of novel thiazolidinone derivatives, we have designed and synthesised a series of new compounds containing the 1,3,4-thiadiazole and thiazolidin-4-one.

Results and discussion

Previously the thiazolidin-4-ones were synthesised by the two-step process. First the Schiff bases were designed and prepared by the reaction of substituted amine and substituted benzaldehydes. Second the thiazolidin-4-ones were synthesised by the reaction of the Schiff bases and mercaptoacetic acid.[13]

In this study, the 2-(substitutedphenyl)-3-[5-(substitutedphenyl)-1,3,4-thiadiazol-2-yl] thiazolidin-4-one (**3a–g**) was designed and prepared by the reaction of 5-(substitutedphenyl)-1,3,4-thiadiazol-2-amine (**2a–g**), substituted benzaldehyde and mercaptoacetic acid via a one-pot three-component reaction as shown in Scheme 1. The results are reported in Table 1.

Instrumentation and chemicals

Melting points were reconded on an X-4 binocular microscope melting point apparatus. ^{1}H NMR spectra were recorded on an Avance Bruker-500 instrument and chemical shifts in ppm are reported with TMS as the internal standard. IR spectra in KBr were recorded by a Perkin-Elmer PE-683 infrared spectrometer. Elemental analyses were performed on a Elementer Vario EL III elementary analysis instrument. Crystal structure determination was carried out on a Enraf-Nonius CAD-4 diffractometer.

Table 1 Synthesis of compounds **3a–g**

No.	R^1	R^2	Yield/%
3a	*m*-Methyl	*p*-Methoxy	55
3b	*p*-Fluoro	H	63
3c	3,5-Dimethyl	*p*-Methoxy	57
3d	2,4-Dichloro	H	61
3e	*m*-Trifluoromethyl	H	56
3f	*p*-Methoxy	*p*-Chloro	77
3g	*p*-Methoxy	*p*-Fluoro	70

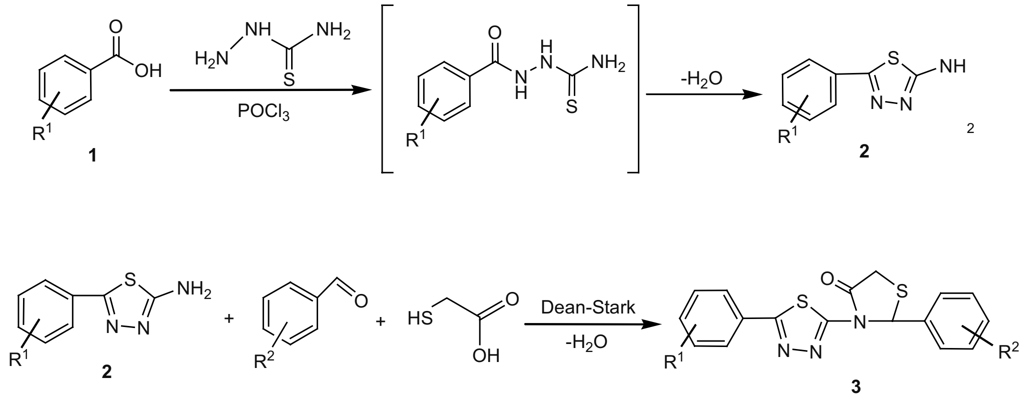
General synthetic procedure for the preparation of **2a–g**

To a mixture of substituted benzoic acid 1(0.1 mol) and thiosemicarbazide (0.1 mol) was added $POCl_3$ (0.3 mol) dropwise at 0–5 °C and maintained for 30 min. The reaction mixture was heated until reflux and stirred for 4 h. After cooling, 50 mL water was added to the reaction mixture. The pH of the reaction solution was adjusted to the range of 8–9 with the solution of 50% NaOH. The crude product precipitated, filtered, washed with water, dried, and recrystallised from ethanol to afford compound **2a–g**.

General synthetic procedure for the preparation of **3a–g**

An equimolar mixture (5 mmol) of substituted benzaldehydes and **2a–g** in dry toluene (50 mL) was refluxed until no more water was collected in a Dean–Stark water separator. Mercaptoacetic acid (6 mmol) was added, dropwise, to this crude mixture, and the reaction was carried out at reflux temperature until stoichiometric water was collected. After the reaction the mixtures cooled, precipitated, filtered, washed with ethanol, dried, and recrystallised from acetone to afford compound **3a–g**. Crystals of **(3a)** suitable for X-ray diffraction were obtained by slow evaporation of ethanol-acetone mixture solution.

2-(4-Methoxyphenyl)-3-[5-(3-methylphenyl)-1,3,4-thiadiazol-2-yl] thiazolidin-4-one (**3a**): (55%) M.p. 243–244 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ(ppm): 2.38 (s, 3H, CH_3), 3.75 (s, 3H, $-OCH_3$), 3.84, 4.16 (d, 2H, CH_2), 6.71 (s, 1H, CH), 6.83–7.73 (m, 8H, Ph). IR (KBr) ν: 3045, 2962, 2839, 1689, 1652, 1506, 1463, 1303, 1251, 1020,



Scheme 1 Synthesis route of compounds **3a–g**

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690 cm^{-1}. Anal. Calcd for $C_{19}H_{17}N_3O_2S_2$: C, 59.51; H, 4.47; N, 10.96; S, 16.72. Found: C, 59.40; H, 4.35; N, 10.82; S, 16.52%.

2-Phenyl-3-[5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl]thiazolidin-4-one (**3b**): (63%) M.p. 240–242 °C. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ(ppm): 3.84, 4.16 (d, 2H, CH_2), 6.74 (s, 1H, CH), 7.11–7.91 (m, 9H, Ph). IR (KBr) ν: 3074, 2902, 2898, 1683, 1652, 1506, 1456, 1303, 1220, 1103, 705 cm^{-1}. Anal. Calcd for $C_{17}H_{12}FN_3OS_2$: C, 57.13; H, 3.38; N, 11.76; S, 17.94. Found: C, 56.96; H, 3.15; N, 11.58; S, 17.66%.

2-(4-Methoxyphenyl)-3-[5-(3,5-dimethylphenyl)-1,3,4-thiadiazol-2-yl]thiazolidin-4-one (**3c**): (57%) M.p. 190–192 °C. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ(ppm): 2.35 (s, 6H, CH_3), 3.80 (s, 3H, $-OCH_3$), 3.86, 4.17 (d, 2H, CH_2), 6.71 (s, 1H, CH), 6.84–7.53 (m, 7H, Ph). IR (KBr) ν: 3049, 2962, 2835, 1683, 1652, 1506, 1456, 1299, 1242, 1039, 692 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_3O_2S_2$: C, 60.43; H, 4.82; N, 10.57; S, 16.13. Found: C, 60.25; H, 4.69; N, 10.38; S, 16.02%.

2-Phenyl-3-[5-(2,4-dichlorophenyl)-1,3,4-thiadiazol-2-yl] thiazolidin-4-one (**3d**): (61%) M.p. 199–200 °C. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ(ppm): 3.84, 4.18 (d, 2H, CH_2), 6.75 (s, 1H, CH), 6.28–8.19 (m, 8H, Ph). IR (KBr) ν: 3064, 2985, 1704, 1652, 1506, 1456, 1315, 1107, 1060, 707 cm^{-1}. Anal. Calcd for $C_{17}H_{11}Cl_2N_3OS_2$: C, 50.01; H, 2.72; N, 10.29; S, 15.70. Found: C, 49.86; H, 2.66; N, 10.12; S, 15.54%.

2-phenyl-3-[5-(3-trifluoromethylphenyl)-1,3,4-thiadiazol-2-yl] thiazolidin-4-one **3e**: (56%) M.p. 203–204 °C. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ(ppm): 3.88, 4.20 (d, 2H, CH_2), 6.76 (s, 1H, CH), 7.26–8.20 (m, 9H, Ph). IR (KBr) ν: 3078, 2979, 1697, 1652, 1506, 1448, 1330, 1311, 1130, 685 cm^{-1}. Anal. Calcd for $C_{18}H_{12}F_3N_3OS_2$: C, 53.06; H, 2.97; N, 10.31; S, 15.74. Found: C, 52.91; H, 2.82; N, 10.16; S, 15.65%.

2-(4-Chlorophenyl)-3-[5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-yl] thiazolidin-4-one **3f**: (77%) M.p. 213–214 °C. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ(ppm): 3.83 (s, 3H, $-OCH_3$), 3.88, 4.12 (d, 2H, CH_2), 6.67 (s, 1H, CH), 6.67–7.84 (m, 8H, Ph). IR (KBr) ν: 3082, 2947, 1683, 1652, 1506, 1463, 1309, 1253, 1180, 1081, 603 cm^{-1}. Anal. Calcd for $C_{18}H_{14}ClN_3O_2S_2$: C, 53.53; H, 3.49; N, 10.40; S, 15.88. Found: C, 53.35; H, 3.18; N, 10.18; S, 15.63%.

Table 2 Crystal data and structure refinement for $C_{19}H_{17}N_3O_2S_2$

Empirical formula	$C_{19}H_{17}N_3O_2S_2$
Formula weight	383.48 g mol^{-1}
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2_1
Unit cell dimensions	8.5850(17)Å 7.3680(15)Å β = 95.35(3) 14.067(3)Å
Volume	885.9(3) $Å^{-3}$
Z	2
Absorption correction	Psi-scan
F(000)	400
Absorption coefficient	0.302 mm^{-1}
θrange for entire data collection	1.45°to 25.97°
Reflections collected	2344
Independent reflections	2168 (R_{int} = 0.0189)
Data/restraints/parameters	2168/1/235
Final R indices [I>2σ>(I)]	R^1 = 0.0515, wR^2 = 0.1358
	R^1 = 0.0615, wR^2 = 0.1460
Goodness-of-fit on F^2	1.066
Final residual electron density	0.343 and –0.435 e. $Å^{-3}$

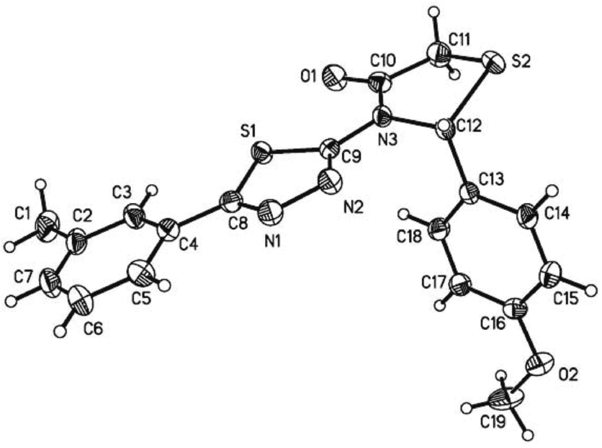

Fig. 1 A view of the molecular structure of **3a**, showing atom displacement ellipsoids at the 50% level.

2-(4-Fluorophenyl)-3-[5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-yl] thiazolidin-4-one **3g**: (70%) M.p. 176–178 °C. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ(ppm): 3.84 (s, 3H, $-OCH_3$), 3.86, 4.15 (d, 2H, CH_2), 6.70 (s, 1H, CH), 6.94–7.85 (m, 8H, Ph). IR (KBr) ν: 3024, 2985, 1689, 1652, 1506, 1463, 1309, 1253, 1220, 1031, 669 cm^{-1}. Anal. Calcd for $C_{18}H_{14}FN_3O_2S_2$: C, 55.80; H, 3.64; N, 10.85; S, 16.55. Found: C, 55.66; H, 3.45; N, 10.69; S, 16.35%.

The compound (**3a**) was subjected to single crystal X-ray crystallography and intensity data were collected at 298(2) K on an Enraf-Nonius CAD-4 diffractometer and use graphite Monochromated MoK_α adiation (λ = 0.71073Å). The structure was solved by a direct method using the SHELXL-97 program[14] and refined with the SHELXL-97 program.[15] All H atoms bonded to the C atoms were placed geometrically at the distances of 0.93–0.97 Å and included in the refinement in riding motion approximation with $U_{iso}(H)$ = 1.2 or 1.5U_{eq} of the carrier atom. The thermal ellipsoids were plotted with the SHELXL-97 program at 50% probability. The molecular structure is shown in Fig. 1. Selected crystal data and structure refinement details are presented in Table 2. Selected bond distances and angles are listed in Table 3.

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Table 3 Selected bond distances (Å) and angles (°) for compound **(3a)**

S1 C8 1.719(5)	N1 N2 1.366(7)	C2 C3 1.395(8)
S1 C9 1.722(5)	N1 C8 1.299(6)	C2 C7 1.364(9)
S2 C11 1.798(6)	N2 C9 1.294(5)	C3 C4 1.395(8)
S2 C12 1.840(5)	N3 C9 1.377(6)	C4 C5 1.376(8)
O1 C10 1.224(6)	N3 C10 1.360(5)	C4 C8 1.451(7)
O2 C16 1.346(6)	N3 C12 1.458(6)	C5 C6 1.367(10)
O2 C19 1.413(8)	C1 C2 1.494(9)	C6 C7 1.375(10)
C8 S1 C9 85.9(2)	S1 C8 N1 113.8(4)	N3 C10 C11 111.8(4)
C11 S2 C12 91.8(2)	S1 C8 C4 121.7(4)	S2 C11 C10 108.1(4)
C16 O2 C19 117.9(4)	N1 C8 C4 124.4(4)	S2 C12 N3 103.1(3)
N2 N1 C8 113.8(4)	S1 C9 N2 115.8(4)	S2 C12 C13 113.9(3)
N1 N2 C9 110.6(4)	S1 C9 N3 123.5(3)	N3 C12 C13 112.7(4)
C9 N3 C10 121.6(4)	N2 C9 N3 120.7(4)	O2 C16 C15 115.1(4)
C9 N3 C12 119.1(3)	O1 C10 N3 123.7(5)	O2 C16 C17 124.6(5)
C10 N3 C12 118.3(4)	O1 C10 C11 124.5(4)	C15 C16 C17 120.2(4)

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