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Note

Synthesis of novel 2-phenylsulfonylhydrazono-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)thiazolidine-4-ones from thiosemicarbazide precursors

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Abstract—To develop novel biologically active organic compounds possessing a sugar moiety, a series of 2-phenylsulfonylhydrazono-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)thiazolidine-4-one were synthesized *via* reaction of the thiosemicarbazide with ethyl bromoacetate. Their chemical structures were characterized by ^{1}H and ^{13}C NMR spectroscopy, elemental analysis and MS. The bioassay results indicated that some of these compound exhibit moderate fungicidal and herbicidal activities. Furthermore, the effect of various solvents at reflux temperature on the reactions of ethyl bromoacetate with the related thiosemicarbazides was investigated.

Keywords: Thiosemicarbazide; Thiazolidine-4-one; Fungicide

Thiazolidine-4-one represents a prevalent scaffold in drug discovery.[1] A survey of the most recent literature indicate that chemicals containing this moiety are potential antibacterial,[2] antimycobacterial,[3] anticonvulsant,[4] antiparasitic,[5] anti-inflammatory,[6] analgesic[7] and herbicidal[8] agents. Moreover, it has been reported that thiourea can serve as the precursor of thiazolidine-4-one derivatives.[9,10]

Interestingly, Garnaik et al. reported that several 2-(arylimino)-4-tetra-*O*-acetyl-β-D-glucopyranosyl-4-thiazolidinones showed promising antimicrobial and antifungal activities.[11] Yet carbohydrates linked with phenylsulfonylated hydrazines or thiazolidine-4-ones have not been reported. As part of our program aimed at developing potential agrochemicals, we designed and synthesized the title compounds and studied their bioactivities.

Previously, we have described the syntheses of 1-arylsulfonyl-4-(*N*-2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazides (**2a**–**h**) *via* condensation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate with substituted phenylsulfonyl hydrazines.[12] In the present study, novel products 2-phenylsulfonylhydrazono-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-thiazolidine-4-ones (**3a**–**d**) and 2-phenylsulfonylhydrazono-3-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)thiazolidine-4-ones (**3e**–**h**) were synthesized by reactions of (**2a**–**h**) with ethyl bromoacetate. The synthetic route for (**3a**–**h**) is described in Scheme 1.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate and 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl isothiocyanate (**1a**,**b**) were prepared according to the literature procedures.[13,14] The common method for the synthesis of thiosemicarbazide compounds involved the reaction of isothiocyanate with hydrazine in ethanol or acetonitrile. We applied this strategy to synthesize 1-arysulfonyl thiosemicarbazides (**2a**–**h**). Interestingly, we found that the condensation of (**1a**,**b**) with phenylsulfonyl hydrazines requires 10–24 h at room temperature or 4–8 h at reflux.

In order to obtain thiazolidine-4-one, Saleh et al. cyclized substituted thiourea with chloroacetic acid in the presence of weak base.[15] Cooley's et al.[9] refluxed

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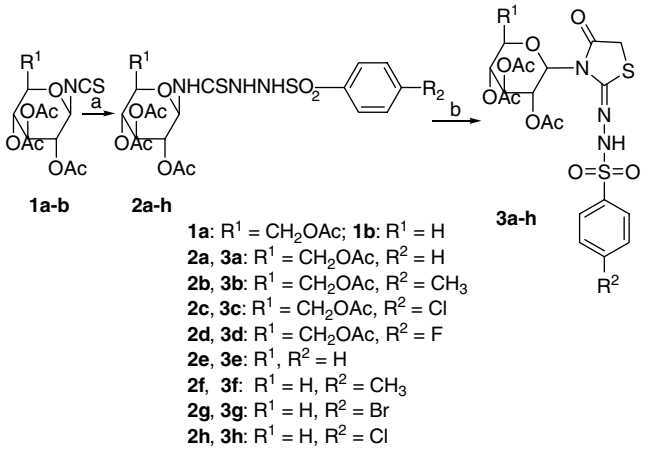

Scheme 1. Reagents and conditions: (a) *p*-R^2–Ph–SO_2NHNH_2, acetonitrile, rt; (b) $CHCl_3$, ethyl bromoacetate, reflux.

thiosemicarbazides with ethyl bromoacetate for 7 days in dichloromethane to give the expected products. We applied this strategy to synthesize our target compounds. At first, we found that the yield of **3a** from **2a** after 7 days was low. To optimize the reaction conditions at this step, the reaction medium and time were investigated. A black oily material was obtained when **2a** and ethyl bromoacetate were refluxed in carbon tetrachloride for 2 h or in 1,2-dichloroethane for 1 h, respectively. The crude products obtained were purified on silica gel column (1:2 EtOAc–petroleum ether), to give **3a** in 65.3% and 46.8% yield, respectively. A summary of the results obtained for the reaction of **2a** with ethyl bromoacetate in different solvents is collected in Table 1.

It appeared that the reaction rate in chloroform was much faster than that in dichloromethane. The yield using chloroform as a solvent was better than that in dichloromethane. Although it is possible that the elevated reaction temperature due to reflux plays an important role in the beneficial effect using chloroform as a reaction medium, we are not able to exclude other factors of these solvents such as polarity effect. Based on the above findings, chloroform was chosen as the reaction medium to synthesize compounds **3b**–**h**.

Compound **2b**, **2e** and **3b** were tested in soil treatment against several herbs such as *Brassica campestris*, *Echinochloa crus-galli, Amaranthus retroflexus* L. and *Digitaria sanguinalis* (L.) Scop at 1.5 kg/ha.[16] The bioassay results showed that most of them had rather weak herbicidal activities. The inhibitory rate of **3b** against *B. campestris* was 39.8%. Compounds **2b**, **2e** and **3b** were also tested for their in vitro fungicidal activity against *Gibberella zeae*, *Alternaria solani*, *Cercospora arachidicola*, *Physalospora piricola* and *Phoma asparagi* at 50 ppm. The inhibitory rate of **2b**, **2e** and **3b** against *P. piricola* and *P. asparagi* ranged between 30% and 40%.

Table 1. Yields of **3a** in different solvents at reflux temperature

Solvent	Reaction time	Yield (%)
CH_2Cl_2	7 days	61.3
$CHCl_3$	8–10 h	86.7
CCl_4	6 h	65.3
$ClCH_2CH_2Cl$	3 h	46.8

1. Experimental

1.1. General methods

Melting points were measured on a Yanaco MP-500 micro-melting point apparatus. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as a solvent on Bruker AC-400 instrument using Me_4Si as an internal standard. Elemental analysis was performed on a Yanaco CHN Corder MF-3 automatic elemental analyzer. Mass spectra were recorded with VG ZAB-HS using the FAB method.

1.2. Preparation of 2-phenylsulfonylhydrazono-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)thiazolidine-4-ones (3a–h), general method

To a soln of **2a**–**h** (0.5 mmol) in $CHCl_3$ (20 mL), ethyl bromoacetate (0.25 g, 1.5 mmol) was added dropwise with stirring. After stirring for 0.5 h at room temperature, the soln was refluxed for 6 h. Concentration resulted in a crude product, which was purified on a silica gel column (1:2 EtOAc–petroleum ether).

1.3. 2-Phenylsulfonylhydrazono-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)thiazolidine-4-one (3a)

From 0.28 g of **2a** (0.26 g, 86.7%); mp 176–177 °C (recrystallized from EtOAc–petroleum ether to give white crystals); ^1H NMR ($CDCl_3$): δ 8.07–7.60 (m, 5H, Ar–H), 6.66–6.52 (m, 1H, NH), 5.91–5.74 (m, 1H, H-1′), 5.48–5.45 (m, 1H, H-5′), 5.20–4.99 (m, 2H, H-2′, H-3′), 4.20–4.11 (m, 2H, H-6′, H-4′), 3.88–3.67 (m, 3H, H-6′, CH_2S), 2.06, 2.05, 2.00, 1.88 (4s, 12H, 4 × OAc); ^{13}C NMR ($CDCl_3$): δ 170.94 (C-4), 170.28, 170.02, 169.64, 169.30 (4 × C=O), 160.47 (C-2), 137.55, 133.85, 129.45, 128.73 (6 × C–Ar), 80.93 (C-1′), 74.66, 73.62, 67.68, 67.32 (C-2′, C-3′, C-4′, C-5′), 61.90 (C-6′), 32.61 (C-5), 20.93, 20.78, 20.59 (4 × CH_3); FABMS: *m*/*z* 602.3 $[M+H]^+$. Anal. Calcd for $C_{23}H_{27}N_3O_{12}S_2$: C, 45.92; H, 4.52; N, 6.98. Found: C, 45.76; H, 4.49; N, 7.08.

1.4. 2-(4-Methylphenyl)sulfonylhydrazono-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)thiazolidine-4-one (3b)

From 0.29 g of **2b** (0.25 g, 81.2%); mp 175–177 °C (recrystallized from EtOAc–petroleum ether to give

white crystals); ^{1}H NMR ($CDCl_3$): δ 7.95–7.32 (m, 4H, Ar–H), 6.75–6.60 (m, 1H, NH), 5.94–5.78 (m, 1H, H-1′), 5.51–5.48 (m, 1H, H-5′), 5.28–4.97 (m, 2H, H-2′, H-3′), 4.20–4.11 (m, 2H, H-6′, H-4′), 3.79–3.75 (m, 3H, H-6′, CH_2S), 2.46 (s, 3H, CH_3), 2.05, 2.03, 2.00, 1.89 (4s, 12H, $4\times$OAc); ^{13}C NMR ($CDCl_3$): δ 170.93 (C-4), 170.37, 170.03, 169.51, 169.33 ($4\times$C=O), 160.87 (C-2), 144.92, 134.58, 129.95, 129.87, 128.77, 128.44 ($6\times$C–Ar), 80.92 (C-1′), 74.89, 73.73, 67.90, 67.36 (C-2′, C-3′, C-4′, C-5′), 61.95 (C-6′), 32.60 (C-5), 21.88 (CH_3–Ar), 20.90, 20.78, 20.62 ($4\times CH_3$); FABMS: *m/z* 616.1 $[M+H]^+$. Anal. Calcd for $C_{24}H_{29}N_3O_{12}S_2$: C, 46.82; H, 4.75; N, 6.70. Found: C, 46.86; H, 4.43; N, 6.83.

1.5. 2-(4-Chlorophenyl)sulfonylhydrazono-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)thiazolidine-4-one (3c)

From 0.30 g of **2c** (0.21 g, 62.9%); mp 188–190 °C (recrystallized from EtOAc–petroleum ether to give white crystals); ^{1}H NMR ($CDCl_3$): δ 8.02–7.52 (m, 4H, Ar–H), 6.95–6.72 (m, 1H, NH), 5.69–5.65 (m, 1H, H-1′), 5.48–5.44 (m, 1H, H-5′), 5.24–4.88 (m, 2H, H-2′, H-3′), 4.21–4.13 (m, 2H, H-6′, H-4′), 3.89–3.72 (m, 3H, H-6′, CH_2S), 2.09, 2.07, 2.03, 1.86 (4s, 12H, $4\times$OAc); ^{13}C NMR ($CDCl_3$): δ 171.01 (C-4), 170.54, 170.12, 169.63, 169.42 ($4\times$C=O), 158.66 (C-2), 140.42, 136.09, 130.17, 129.78 ($6\times$C–Ar), 80.92 (C-1′), 74.57, 73.44, 67.72, 67.43, 67.12 (C-2′, C-3′, C-4′, C-5′), 61.62 (C-6′), 32.67 (C-5), 20.88, 20.80, 20.57 ($4\times CH_3$); FABMS: *m/z* 636.0 $[M+H]^+$. Anal. Calcd for $C_{23}H_{26}ClN_3O_{12}S_2$: C, 43.43; H, 4.12; N, 6.61. Found: C, 43.48; H, 4.01; N, 6.61.

1.6. 2-(4-Fluorophenyl)sulfonylhydrazono-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)thiazolidine-4-one (3d)

From 0.29 g of **2d** (0.25 g, 82.3%); mp 191–193 °C (recrystallized from EtOAc–petroleum ether to give white crystals); ^{1}H NMR ($CDCl_3$): δ 8.16–7.29 (m, 4H, Ar–H), 6.67–6.49 (m, 1H, NH), 5.64–5.60 (m, 1H, H-1′), 5.47–5.45 (m, 1H, H-5′), 5.24–5.07 (m, 2H, H-2′, H-3′), 4.21–4.13 (m, 2H, H-6′, H-4′), 3.90–3.77 (m, 3H, H-6′, CH_2S), 2.11, 2.08, 2.01, 1.87 (4s, 12H, $4\times$OAc); ^{13}C NMR ($CDCl_3$): δ 170.97 (C-4), 170.45, 170.06, 169.69, 169.31 ($4\times$C=O), 164.81 (C-2), 158.24, 133.50, 131.71, 131.51, 117.00, 116.77 ($6\times$C–Ar), 80.92 (C-1′), 74.54, 73.48, 67.41, 67.05 (C-2′, C-3′, C-4′, C-5′), 61.61 (C-6′), 32.70 (C-5), 20.90, 20.78, 20.60 ($4\times CH_3$); FABMS: *m/z* 620.0 $[M+H]^+$. Anal. Calcd for $C_{23}H_{26}FN_3O_{12}S_2$: C, 44.59; H, 4.23; N, 6.78. Found: C, 44.69; H, 4.12; N, 6.82.

1.7. 2-Phenylsulfonylhydrazono-3-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)thiazolidine-4-one (3e)

From 0.25 g of **2e** (0.18 g, 65.6%); mp 190–192 °C (recrystallized from EtOAc–petroleum ether to give white crystals); ^{1}H NMR ($CDCl_3$): δ 7.93–7.58 (m, 5H, Ar–H), 7.02 (s, 1H, NH), 5.77–4.81 (m, 4H, H-2′, H-3′, H-4′, H-1′), 4.08–4.06 (m, 1H, H-5′), 3.81–3.71 (m, 2H, CH_2S), 3.32–3.27 (m, 1H, H-5′), 2.02, 2.01, 1.90 (3s, 9H, $3\times$OAc); ^{13}C NMR ($CDCl_3$): δ 171.03 (C-4), 170.20, 169.97, 169.83 ($3\times$C=O), 164.43 (C-2), 137.51, 133.88, 129.20, 128.74 ($6\times$C–Ar), 81.75 (C-1′), 73.08, 68.57, 67.69, 65.50 (C-2′, C-3′, C-4′, C-5′), 32.60 (C-5), 20.97, 20.84, 20.59 ($3\times CH_3$); FABMS: *m/z* 530.0 $[M+H]^+$. Anal. Calcd for $C_{20}H_{23}N_3O_{10}S_2$: C, 45.36; H, 4.38; N, 7.94. Found: C, 45.65; H, 4.54; N, 8.22.

1.8. 2-(4-Methylphenyl)sulfonylhydrazono-3-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)thiazolidine-4-one (3f)

From 0.25 g of **2f** (0.20 g, 71.5%); mp 190–191 °C (recrystallized from EtOAc–petroleum ether to give white crystals); ^{1}H NMR ($CDCl_3$): δ 7.86–7.40 (m, 5H, Ar–H), 6.47 (s, 1H, NH), 5.83–4.86 (m, 4H, H-2′, H-3′, H-4′, H-1′), 4.16–4.12 (m, 1H, H-5′), 3.84–3.73 (m, 2H, CH_2S), 3.35–3.33 (m, 1H, H-5′), 2.46 (s, 3H, CH_3), 2.05, 2.04, 1.96 (3s, 9H, $3\times$OAc); ^{13}C NMR ($CDCl_3$): δ 171.03 (C-4), 170.21, 169.81 ($3\times$C=O), 164.92 (C-2), 144.92, 134.51, 129.81, 128.77 ($6\times$C–Ar), 81.80 (C-1′), 68.57, 67.71, 65.59, 61.95 (C-2′, C-3′, C-4′, C-5′), 32.61 (C-5), 21.84 (CH_3–Ar), 20.89, 20.66 ($3\times CH_3$); FABMS: *m/z* 544.0 $[M+H]^+$. Anal. Calcd for $C_{21}H_{25}N_3O_{10}S_2$: C, 46.40; H, 4.64; N, 7.73. Found: C, 46.47; H, 4.70; N, 7.53.

1.9. 2-(4-Bromophenyl)sulfonylhydrazono-3-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)thiazolidine-4-one (3g)

From 0.28 g of **2g** (0.22 g, 72.3%); mp 174–176 °C (recrystallized from EtOAc–petroleum ether to give white crystals); ^{1}H NMR ($CDCl_3$): δ 7.85–7.75 (m, 4H, Ar–H), 6.77 (s, 1H, NH), 5.77–4.83 (m, 4H, H-2′, H-3′, H-4′, H-1′), 4.16–4.12 (m, 1H, H-5′), 3.85–3.74 (m, 2H, CH_2S), 3.37–3.32 (m, 1H, H-5′), 2.06, 2.05, 1.94 (3s, 9H, $3\times$OAc); ^{13}C NMR ($CDCl_3$): δ 170.87 (C-4), 170.18, 169.88 ($3\times$C=O), 169.81 (C-2), 136.56, 132.57, 130.30, 129.11 ($6\times$C–Ar), 81.77 (C-1′), 72.98, 68.54, 67.69, 65.54 (C-2′, C-3′, C-4′, C-5′), 32.64 (C-5), 20.97, 20.84, 20.62 ($3\times CH_3$); FABMS: *m/z* 608.0 $[M+H]^+$. Anal. Calcd for $C_{20}H_{22}BrN_3O_{10}S_2$: C, 39.48; H, 3.64; N, 6.91. Found: C, 39.28; H, 3.79; N, 7.10.

1.10. 2-(4-Chlorophenyl)sulfonylhydrazono-3-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)thiazolidine-4-one (3h)

From 0.26 g of **2h** (0.18 g, 65%); mp 170–171 °C (recrystallized from EtOAc–petroleum ether to give white crystals); ^{1}H NMR ($CDCl_3$): δ 7.94–7.60 (m, 4H, Ar–H), 6.66 (s, 1H, NH), 577–4.84 (m, 4H, H-2′, H-3′, H-4′, H-1′), 4.17–4.13 (m, 1H, H-5′), 3.81–3.79 (m, 2H,

CH_2S), 3.38–3.38 (m, 1H, H-5′), 2.06, 2.04, 1.95 (3s, 9H, $3\times$OAc); ^{13}C NMR ($CDCl_3$): δ 170.78 (C-4), 170.15, 169.88 ($3\times$C=O), 169.75 (C-2), 140.57, 136.01, 130.24, 129.60 ($6\times$C–Ar), 81.80 (C-1′), 72.99, 68.52, 67.68, 20.62, 65.58 (C-2′, C-3′, C-4′, C-5′), 32.59 (C-5), 20.84–20.63 ($3\times CH_3$); FABMS: m/z 564.0 $[M+H]^+$. Anal. Calcd for $C_{20}H_{22}ClN_3O_{10}S_2$: C, 42.59; H, 3.93; N, 7.45. Found: C, 42.31; H, 3.90; N, 7.67.

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