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FACILE SYNTHESIS OF NEW (*Z*)-6-ARYLMETHYLIDENE-1,3,4-THIADIAZIN-5(6*H*)-ONE DERIVATIVES

3-Aryl-2-sulfanylpropenoic acids reacted with acetohydrazonyl chlorides in refluxing absolute ethanol in the presence of equimolar amount of triethylamine forming (*Z*)-6-arylmethylidene-1,3,4-thiadiazin-5-one derivatives. X-Ray study on the crystal of one of the obtained products was carried out.

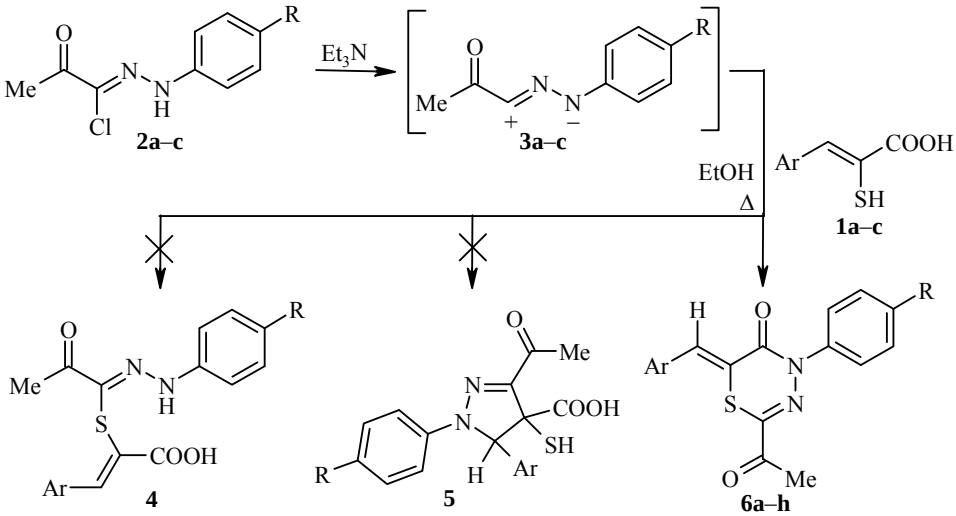
Keywords: *N*'-arylacetonitrilimines, (*Z*)-6-arylmethylidene-1,3,4-thiadiazin-5(6*H*)-one derivatives, 3-aryl-2-sulfanylpropenoic acids.

The synthetic utility of 3-aryl-2-sulfanylpropenoic acids has been well-known for more than a century. They have been widely used as versatile intermediates for the synthesis of nitriles, amino acids, α-thio acids [1], and thiazoles [2–4]. In addition, 3-aryl-2-sulfanylpropenoic acids are known as antidotes for heavy metal poisoning [5–7].

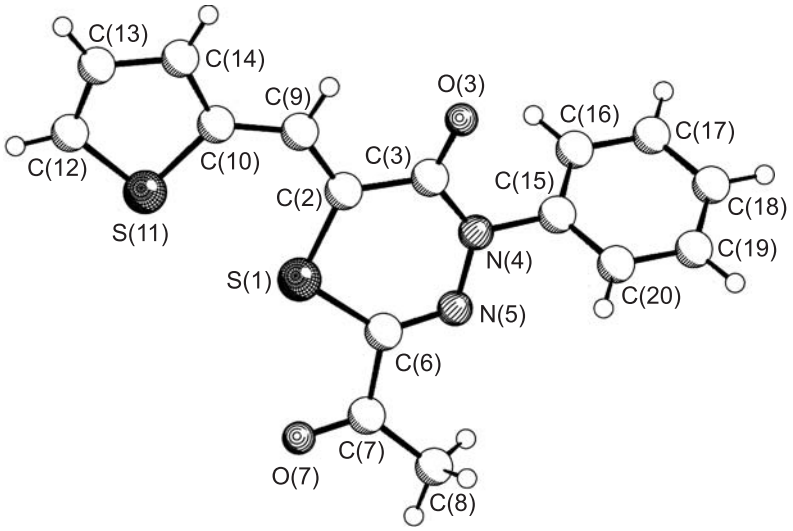
It is well-known that 1,3,4-thiadiazinone derivatives have attracted a great deal of interest due to a variety of interesting biological activities. They are known as spasmolytic [8] and antibacterial agents [9], important matrix metalloproteinase inhibitors [10, 11], and they also display cardiotonic, hypertensive [12, 13], and other biological activities [14–16].

In continuation of our interest in synthesis of some new heterocyclic compounds with biological activity [17–24], we report here a simple preparation of (*Z*)-6-arylmethylidene-1,3,4-thiadiazin-5-one derivatives *via* one-step reaction of 3-aryl-2-sulfanylpropenoic acids with hydrazonyl chlorides.

The reaction of equimolar amounts of 3-aryl-2-sulfanylpropenoic acids **1a–c**, *N*-aryl-substituted acetohydrazonyl chlorides **2a–c** and triethylamine in refluxing



1 a Ar = piperonyl, **b** Ar = 2-thienyl, **c** Ar = 2-furyl; **2**, **3 a** R = H, **b** R = Me, **c** R = Cl; **6a** R = H, Ar = piperonyl; **b** R = H, Ar = 2-thienyl; **c** R = H, Ar = 2-furyl; **d** R = Me, Ar = piperonyl; **e** R = Me, Ar = 2-thienyl; **f** R = Cl, Ar = piperonyl; **g** R = Cl, Ar = 2-thienyl; **h** R = Cl, Ar = 2-furyl



Molecular structure of compound **6b**

absolute ethanol afforded stable adducts. The IR spectra of the isolated products showed two absorption bands in each case in the region of 1667–1697 cm^{-1} due to two carbonyl groups. Thus the IR spectra of the isolated products supported the formation of cyclic structures **5** or **6** and ruled out structure **4** by the absence of NH and OH absorption bands. The ^{1}H NMR spectra in each case revealed a singlet signal at 2.60–2.66 ppm due to acetyl protons in addition to a singlet signal at ~8.0 ppm attributable to olefinic protons. The mass spectrum of compound **6b** taken as a typical example of the prepared series showed a molecular ion peak at *m*/*z* 328 $[M]^+$. From the above data, as well as elemental analyses, structures **6a**–**h** were assigned to these products, and the structure **5** was ruled out. An additional evidence was obtained from the X-ray crystallography of compound **6b** (Figure), which showed that the structure has *Z*-configuration. It should be mentioned that the reaction of hydrazonyl halides with thioglycolic acid or its derivatives afforded the same thiadiazinones, but with *E*-configuration [25, 26].

Thus, an efficient and simple one-step route for the synthesis of (*Z*)-6-aryl-methylidene-1,3,4-thiadiazin-5(6*H*)-one derivatives from the reaction of 3-aryl-2-sulfanylpropenoic acids and *N*'-arylacetonitrilimines is described.

EXPERIMENTAL

The IR spectra were recorded in KBr pellets on a Perkin Elmer 1430 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer (200 MHz), ^{13}C NMR spectra – on a Varian Gemini 300 spectrometer (300 MHz). All NMR spectra are registered in DMSO-d_6 using TMS as internal standard. Electron ionization mass spectra were recorded on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalysis Center of Cairo University, Giza, Egypt. Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. The X-ray crystallography was carried out in the Institute of Organic Chemistry, Technical University of Dresden, Germany.

The starting compounds **1a**–**c** [27] and hydrazonyl chlorides **2a**–**c** [28] were prepared according to published procedures.

The Reaction of 3-Aryl-2-sulfanylpropenoic Acids with Hydrazonyl Chlorides (General Method). A mixture of 3-aryl-2-sulfanylpropenoic acids **1a**–**c** (0.01 mol) and appropriate hydrazonyl chlorides **2a**–**c** (0.01 mol) was stirred under reflux in abs. EtOH

(30 ml) with Et_3N (0.01 mol) for 10 h. The solvent was evaporated under reduced pressure. The precipitate that formed was filtered off and recrystallized from AcOH.

(*Z*)-2-Acetyl-6-(benzo[1,3]dioxol-5-ylmethylidene)-4-phenyl-4*H*-1,3,4-thiadiazin-5(6*H*)-one (6a). Yield 2.6 g (71%). Pale yellow crystals. Mp 210–211°C. IR spectrum, ν, cm^{-1}: 1670, 1680 (CO). ^1H NMR spectrum, δ, ppm: 2.65 (3H, s, CH_3); 6.17 (2H, s, CH_2); 6.80–7.18 (8H, m, H Ar); 8.05 (1H, s, ArC<u>H</u>). Mass spectrum, *m/z* (I_{rel}, %): 366 $[M]^+$ (39). Found, %: C 62.49; H 3.63; N 7.83; S 8.55. $C_{19}H_{14}N_2O_4S$. Calculated, %: C 62.29; H 3.85; N 7.65; S 8.75.

(*Z*)-2-Acetyl-4-phenyl-6-(thiophen-2-ylmethylidene)-4*H*-1,3,4-thiadiazin-5(6*H*)-one (6b). Yield 2.2 g (67%). Yellow crystals. Mp 178–179°C. IR spectrum, ν, cm^{-1}: 1667, 1681 (CO). ^1H NMR spectrum, δ, ppm: 2.66 (3H, s, CH_3); 7.20–7.90 (8H, m, H Ar); 8.01 (1H, s, ArC<u>H</u>). ^{13}C NMR spectrum, δ, ppm: 192.9 (C=O); 160.5 (C=O); 146.0 (C=N); 142.3; 141.0; 135.1; 132.6; 129.0; 128.7; 128.1; 125.4; 115.6 (C Ar); 110.0 (Ar<u>C</u>H); 26.6 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 328 $[M]^+$ (46). Found, %: C 58.70; H 3.51; N 8.70; S 19.37. $C_{16}H_{12}N_2O_2S_2$. Calculated, %: C 58.52; H 3.68; N 8.53; S 19.53.

(*Z*)-2-Acetyl-6-(furan-2-ylmethylidene)-4-phenyl-4*H*-1,3,4-thiadiazin-5(6*H*)-one (6c). Yield 2.0 g (64%). Yellow crystals. Mp 167–168°C (mp 148°C [26]). IR spectrum, ν, cm^{-1}:1680, 1697 (CO). ^1H NMR spectrum, δ, ppm: 2.61 (3H, s, CH_3); 6.90–7.92 (8H, m, H Ar); 8.04 (1H, s, ArC<u>H</u>). Mass spectrum, *m/z* (I_{rel}, %): 312 $[M]^+$ (34). Found, %: C 61.74; H 3.69; N 8.80; S 10.48. $C_{16}H_{12}N_2O_3S$. Calculated, %: C 61.53; H 3.87; N 8.97; S 10.27.

(*Z*)-2-Acetyl-6-(benzo[1,3]dioxol-5-ylmethylidene)-4-(4-methylphenyl)-4*H*-1,3,4-thiadiazin-5(6*H*)-one (6d). Yield 2.7 g (71%). Pale yellow crystals. Mp 205–206°C. IR spectrum, ν, cm^{-1}: 1678, 1688 (CO). ^1H NMR spectrum, δ, ppm: 2.32 (3H, s, ArC<u>H</u>$_3$); 2.62 (3H, s, $COCH_3$); 6.08 (2H, s, CH_2); 6.83–7.44 (7H, m, H Ar); 7.87 (1H, s, ArC<u>H</u>). Found, %: C 63.36; H 4.05; N 7.59; S 8.61. $C_{20}H_{16}N_2O_4S$. Calculated, %: C 63.15; H 4.24; N 7.36; S 8.43.

(*Z*)-2-Acetyl-6-(thiophen-2-ylmethylidene)-4-(4-methylphenyl)-4*H*-1,3,4-thiadiazin-5(6*H*)-one (6e). Yield 2.3 g (67%). Yellow crystals. Mp 179–180°C. IR spectrum, ν, cm^{-1}: 1673, 1687 (CO). ^1H NMR spectrum, δ, ppm: 2.35 (3H, s, ArC<u>H</u>$_3$); 2.65 (3H, s, $COCH_3$); 7.23–8.06 (7H, m, H Ar); 8.10 (1H, s, ArC<u>H</u>). Mass spectrum, *m/z* (I_{rel}, %): 342 $[M]^+$ (40). Found, %: C 59.85; H 4.30; N 8.40; S 18.55. $C_{17}H_{14}N_2O_2S_2$. Calculated, %: C 59.63; H 4.12; N 8.18; S 18.73.

(*Z*)-2-Acetyl-6-(benzo[1,3]dioxol-5-ylmethylidene)-4-(4-chlorophenyl)-4*H*-1,3,4-thiadiazin-5(6*H*)-one (6f). Yield 2.9 g (72%). Yellow crystals. Mp 214–215°C. IR spectrum, ν, cm^{-1}: 1672, 1681 (CO). ^1H NMR spectrum, δ, ppm: 2.65 (3H, s, CH_3); 6.19 (2H, s, CH_2); 6.82–7.68 (7H, m, H Ar); 7.86 (1H, s, ArC<u>H</u>). Found, %: C 57.12; H 3.10; N 6.77; S 8.18. $C_{19}H_{13}ClN_2O_4S$. Calculated, %: C 56.93; H 3.27; N 6.99; S 8.00.

(*Z*)-2-Acetyl-4-(4-chlorophenyl)-6-(thiophen-2-ylmethylidene)-4*H*-1,3,4-thiadiazin-5(6*H*)-one (6g). Yield 2.4 g (66%). Yellow crystals. Mp 187–188°C. IR spectrum, ν, cm^{-1}: 1678, 1684 (CO). ^1H NMR spectrum, δ, ppm: 2.66 (3H, s, CH_3); 7.54–8.00 (7H, m, H Ar); 8.11 (1H, s, ArC<u>H</u>). ^{13}C NMR spectrum, δ, ppm: 193.1 (C=O); 160.3 (C=O); 147.0 (C=N); 142.6; 139.5; 135.6; 133.8; 129.4; 128.6; 128.0; 126.7; 116.3 (C Ar); 110.6 (Ar<u>C</u>H); 26.8 (CH_3). Found, %: C 53.17; H 3.24; N 7.96; S 17.85. $C_{16}H_{11}ClN_2O_2S_2$. Calculated, %: C 52.96; H 3.06; N 7.72; S 17.67.

(*Z*)-2-Acetyl-4-(4-chlorophenyl)-6-(furan-2-ylmethylidene)-4*H*-1,3,4-thiadiazin-5(6*H*)-one (6h). Yield 2.1 g (61%). Yellow crystals. Mp 196–197°C. IR spectrum, ν, cm^{-1}: 1672, 1680 (CO). ^1H NMR spectrum, δ, ppm: 2.60 (3H, s, CH_3); 7.68–8.00 (7H, m, H Ar); 8.07 (1H, s, ArC<u>H</u>). Found, %: C 55.20; H 3.39; N 8.32; S 9.07. $C_{16}H_{11}ClN_2O_3S$. Calculated, %: C 55.42; H 3.20; N 8.08; S 9.25.

X-Ray Structure Investigation of Compound 6b. The X-ray diffraction measurements were carried out at wavelength 0.71073 Å. Crystal parameters for compound **6b**: $C_{16}H_{12}N_2O_2S_2$; *M* 328.40; crystal system orthorhombic, space group *Pbca*. Unit cell dimensions: *a* 12.158(2), *b* 7.391(2), *c* 33.885(7) Å; α 90, β 90, γ 90°; *V* 3044.9(12) $Å^3$; *T* –75(2)°C; *Z* 8; d_{calc} 1.433 g/cm^{-3}; μ 0.357 cm^{-1}. 45297 reflections are measured, $[sin(\theta)/\lambda]_{max}$ 0.64°·$Å^{-1}$ / 99.8%; R_w2 factor 0.100; ρ 0.53 (–0.37) e·$Å^{-3}$. Crystallographic data of compound **6b** have been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 746860).

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