Research Article

Alkylation and 1,3-Dipolar Cycloaddition of 6-Styryl-4,5-dihydro-2H-pyridazin-3-one: Synthesis of Novel N-Substituted Pyridazinones and Triazolo[4,3-b]pyridazinones

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Some new N-substituted pyridazinones and triazolo[4,3-b]pyridazinones were synthesized, respectively, by simple alkylation and 1,3-dipolar cycloaddition of pyridazin-3-one with nitrile imines. The regioselectivity of the reactions was ascertained by ¹H, ¹³C NMR spectroscopy and X-ray diffraction of the synthesized compounds.

1. Introduction

Pyridazinone derivatives have been reported to exhibit a wide range of pharmacological activities such as antihypertensive [1, 2], anti-HIV [3], antibacterial, [4] aldose reductase inhibitors [5], hepatoprotective agents [6], and COX-2 inhibitors [7]. It has also been reported that pyridazinone derivatives have remarkable anticancer activity [8, 9]. Recently, our research group has reported the synthesis and the antiproliferative activities of new pyridazinone derivatives. Some of these compounds exhibited significant cytotoxicity against human and murine cell lines (A2780, A549, P388, and P815) [10, 11]. As a part of our program we focused on pyridazinones with biological activity, and in connection with our interest in the chemistry of annelated pyridazinones [10–12], in this paper we report the synthesis of a new series of N-substituted pyridazinones and triazolo[4,3-b]pyridazinones, which were obtained, respectively, by alkylation and 1,3-dipolar cycloaddition of 6-styryl-4,5-dihydro-2H-pyridazin-3-one.

2. Experimental Section

Melting points were determined using a Büchi-Tottoli apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded in CDCl₃ or DMSO-d₆ and solution (unless otherwise specified) with TMS as an internal reference using a Bruker AC 300 (¹H) or 75 MHz (¹³C) instruments. Chemical shifts are given in δ parts per million (ppm). Multiplicities of ¹³C NMR resources were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. IR spectra were recorded on a Perkin-Elmer 577 spectrometer (Perkin-Elmer, USA) using KBr disks; only noteworthy IR absorptions are listed (cm⁻¹). High resolution mass spectra were recorded on an Agilent ESI-TOF mass spectrometer. Column chromatography was carried out on SiO₂ (silica gel 60 Merck 0.063–0.200 mm). Thin-layer chromatography (TLC) was carried out on SiO₂ (silica gel 60, F 254 Merck 0.063–0.200 mm), and the spots were located with UV light (254 nm). Commercial reagents were used without further

purification unless stated. Compounds **4a,b** were prepared according to the literature methods [13, 14].

2.1. Synthesis of Pyridazin-3-ones 4a,b. A mixture of the appropriate aldehyde (4 mmol), levulinic acid (4 mmol, 0.46 g), morpholine (3 drops), and glacial acetic acid (9 drops) was heated in toluene at 60 °C for 12 h. The solvent was evaporated; the reaction mixture was cooled and washed with acetic acid : water (1 : 4). In each case the formed precipitate was filtered and dried to give the corresponding compound **3**. A solution of each compound **3a,b** (4.3 mmol) in 20 mL of glacial acetic acid containing hydrazine hydrate (0.5 g, 10 mmol) was heated at reflux for 30 h. The acetic acid was evaporated under vacuum and the residue was taken up with cold water. The precipitate was filtered, washed with cold water, dried, and purified by column chromatography (EtOAc/hexane 4/6).

2.2. 6-Styryl-4,5-dihydro-2H-pyridazin-3-one (4a). Yield: 65%; mp: 160–162 °C; IR (KBr, cm⁻¹): 3420–3350 (NH), 1680 (CO); ¹H NMR (DMSO-d₆): δ 2.42 (t, 2H, CH₂, J = 7.8 Hz), 2.78 (t, 2H, CH₂, J = 7.8 Hz), 6.88 (d, 1H, J = 16.6 Hz), 7.05 (d, 1H, J = 16.6 Hz), 7.27–7.41 (m, 3H, ArH), 7.57–7.60 (m, 2H, ArH), 10.89 (s, 1H, NH); ¹³C NMR (DMSO-d₆): 20.6 (CH₂), 26.3 (CH₂), 126.8 (CH-vinyl), 127.4 (2CH), 128.9 (CH), 129.3 (2CH), 133.9 (CH-vinyl), 136.5 (C), 151.2 (C), 167.7 (CO).

2.3. 6-[2-(4-Methoxyphenyl)vinyl]-4,5-dihydro-2H-pyridazin-3-one (4b). Yield: 62%; mp: 164–166 °C; IR (KBr, cm⁻¹): 3450–3350 (NH), 1685 (C=O); ¹H NMR (DMSO-d₆): δ 2.38 (t, 2H, CH₂, J = 7.6 Hz), 2.75 (t, 2H, CH₂, J = 7.6 Hz), 3.78 (s, 3H, CH₃O), 6.74 (d, 1H, J = 16.8 Hz), 6.92 (d, 2H, J = 8.7 Hz), 6.98 (d, 1H, J = 16.8 Hz), 7.50 (d, 2H, J = 8.7 Hz), 10.80 (s, 1H, NH); ¹³C NMR (DMSO-d₆): 20.6 (CH₂), 26.4 (CH₂), 55.6 (CH₃O), 114.7 (2CH), 124.6 (CH-vinyl), 128.8 (2CH), 129.2 (C), 133.6 (CH-vinyl), 151.4 (C), 160.1 (C), 167.7 (CO).

2.4. Synthesis of N-Substituted Pyridazinones 5a–c. To a solution of compound **4a** (1.22 g, 6.13 mmol) in dry THF (30 mL) was added potassium carbonate (2.50 g, 18.30 mmol). The selected alkyl halide (7.40 mmol) was added dropwise. Upon disappearance of the starting material as indicated by TLC, the solvent was evaporated under vacuum. The crude material was dissolved with CH₂Cl₂ (50 mL), washed with water and brine, dried over MgSO₄ and the solvent was evaporated at reduced pressure. The resulting residue was purified by column chromatography (EtOAc/hexane 3/7).

2.5. 2-Methyl-6-styryl-4,5-dihydro-2H-pyridazin-3-one (5a). Yield: 85%; mp: 136–138 °C; IR (KBr, cm⁻¹): 1666 (CO); ¹H NMR (CDCl₃): δ 2.53 (t, 2H, CH₂, J = 7.4 Hz), 2.79 (t, 2H, CH₂, J = 7.4 Hz), 3.45 (s, 3H, NCH₃), 6.84 (d, 1H, J = 16.5 Hz), 6.93 (d, 1H, J = 16.5 Hz), 7.24–7.48 (m, 5H); ¹³C NMR (CDCl₃): δ 21.2 (CH₂), 26.8 (CH₂), 36.6 (NCH₃), 126.8 (CH-vinyl), 127.4 (2CH), 128.7 (CH), 128.9 (2CH), 134.5

(CH-vinyl), 135.8 (C), 151.7 (C), 165.8 (CO); HRMS (ESI-TOF) *m/z*: calculated for C₁₃H₁₅N₂O [M + H]⁺: 215.11844 found: 215.11816.

2.6. 2-Allyl-6-styryl-4,5-dihydro-2H-pyridazin-3-one (5b). Yield: 72%; mp: 178–180 °C; IR (KBr, cm⁻¹): 1670 (CO); ¹H NMR (CDCl₃): δ 2.57 (t, 2H, CH₂, J = 7.5 Hz), 2.81 (t, 2H, CH₂, J = 7.5 Hz), 4.41–4.44 (m, 2H, NCH₂), 5.18–5.26 (m, 2H, =CH₂), 5.86–5.97 (m, 1H, =CH), 6.86 (d, 1H, J = 16.5 Hz), 6.94 (d, 1H, J = 16.5 Hz), 7.31–7.39 (m, 3H), 7.46–7.50 (m, 2H); ¹³C NMR (CDCl₃): δ 21.1 (CH₂), 26.9 (CH₂), 50.9 (NCH₂), 117.0 (=CH₂), 126.1 (CH), 127.0 (2CH), 128.4 (CH), 128.9 (2CH), 132.8 (CH), 134.4 (CH), 135.8 (C), 151.9 (C), 165.4 (CO); HRMS (ESI-TOF) *m/z*: calculated for C₁₅H₁₇N₂O [M + H]⁺: 241.13950 found: 241.13936.

2.7. 2-(2-Oxo-2-phenylethyl)-6-styryl-4,5-dihydro-2H-pyridazin-3-one (5c). Yield: 60%; mp: 88–90 °C; IR (KBr, cm⁻¹): 1675 (CO), 1690 (CO); ¹H NMR (CDCl₃): δ 2.67 (t, 2H, CH₂, J = 7.6 Hz), 2.91 (t, 2H, CH₂, J = 7.6 Hz), 5.25 (s, 2H, NCH₂), 6.85 (d, 1H, J = 16.5 Hz), 6.92 (d, 1H, J = 16.5 Hz), 7.29–7.38 (m, 3H), 7.45–7.52 (m, 4H), 7.57–7.62 (m, 1H), 7.96–8.00 (m, 2H); ¹³C NMR (CDCl₃): δ 21.2 (CH₂), 26.6 (CH₂), 55.2 (NCH₂), 125.9 (CH), 127.1 (2CH), 128.0 (2CH), 128.4 (CH), 128.7 (2CH), 128.9 (2CH), 133.6 (CH), 134.6 (CH), 135.0 (C), 135.8 (C), 152.2 (C), 166.5 (CO), 192.9 (CO). HRMS (ESI-TOF) *m/z*: calculated for C₂₀H₁₉N₂O₂ [M + H]⁺: 319.14465 found: 319.14438.

2.8. General Procedure for the Preparation of Triazolo[4,3-b]pyridazinones 8a–e. To a solution of pyridazin-3(2H)-one (**4a**) (1.0 g, 5 mmol) and ethyl hydrazono-α-bromoglyoxylate (**6a–e**) (5 mmol) in dry THF (50 mL), K₂CO₃ (2.1 g, 15 mmol) was added. The mixture was refluxed in each case for 5–8 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using Hexane-EtOAc 80 : 20 as eluent.

2.9. 6-Oxo-8a-styryl-1-p-tolyl-1,5,6,7,8,8a-hexahydro-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxylic Acid Ethyl Ester (8a). Yield: 56%; mp: 182–184 °C; IR (KBr, cm⁻¹): 1685 (CONH), 1710 (CO ester), 3050 (NH); ¹H NMR (CDCl₃): δ 1.40 (t, 3H, CH₃, J = 7.2 Hz), 2.28 (s, 3H, CH₃), 2.26–2.39 (m, 3H), 2.78–2.89 (m, 1H), 4.37 (q, 2H, CH₂O, J = 7.2 Hz), 6.49 (d, 1H, J = 16.1 Hz), 6.83 (d, 1H, J = 16.1 Hz), 7.08 (d, 2H, J = 8.4 Hz), 7.22 (d, 2H, J = 8.4 Hz), 7.28–7.39 (m, 3H, ArH), 7.43–7.46 (m, 2H, ArH), 7.53 (s, 1H, NH); ¹³C NMR (CDCl₃): δ 14.2 (CH₃), 20.7 (CH₃), 28.6 (CH₂), 29.5 (CH₂), 62.2 (CH₂O), 88.1 (C-8a), 117.8 (2CH), 127.1 (2CH), 128.7 (2CH), 128.9 (CH), 129.8 (2CH), 133.0 (C), 133.5 (CH), 135.3 (C), 138.4 (C), 140.6 (C), 146.1 (C), 158.2 (CO), 174.3 (CO ester); HRMS (ESI-TOF) *m/z*: calculated for C₂₃H₂₅N₄O₃ [M + H]⁺: 405.19212 found: 405.19201.

2.10. 1-(4-Chloro-phenyl)-6-oxo-8a-styryl-1,5,6,7,8,8a-hexahydro-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxylic Acid Ethyl

TABLE 1: Crystal data and structure refinement parameters of compound **4a**.

Chemical Formula: C ₁₂ H ₁₂ N ₂ O	
Formula weight: 200.24	
Crystal system: monoclinic	Space group (no): <i>P</i> 2 ₁ / <i>n</i> (14)
<i>a</i> = 8.0348 (6) Å	β = 101.074 (2)°
<i>b</i> = 11.1532 (6) Å	<i>V</i> = 1911.5 (3) Å ³
<i>c</i> = 11.9941 (8) Å	<i>Z</i> = 4
<i>D_x</i> = 1.261 Mg m ⁻³	Mo <i>K</i> α radiation, λ = 0.71073 Å
μ = 0.08 mm ⁻¹	<i>F</i> (000) = 424
Crystal sizes = 0.34 * 0.25 * 0.23 mm ³	Crystal: Prism, colourless
No. of reflections collected = 11692	
No. of independent reflections = 2431	No. of reflections with I > 2σ(I) = 1647
θ range for data collection: θ _{max} = 27.5°, θ _{min} = 2.5°	
Goodness-of-ft on <i>F</i> 2 = 1.07	
<i>R</i> indices [I > 2σ(I)]: <i>R</i> 1 = 0.054, <i>wR</i> 2 = 0.179	
(<i>D/s</i>)max = 0.000	(<i>Dr</i>)max = 0.527 eÅ ⁻³ (<i>Dr</i>)min = -0.349 eÅ ⁻³
Measurement: X8 Apex, Bruker CCD	Program system: Apex 2
Structure determination: WinGX (SHELXL and SHELXS)	

TABLE 2: Crystal data and structure refinement parameters of compound **5a**.

Chemical Formula: C ₁₃ H ₁₄ N ₂ O	
Formula weight: 214.26	
Crystal system: monoclinic	Space group: <i>P</i> 2 ₁
<i>a</i> = 6.1966 (3) Å	β = 96.035 (4)°
<i>b</i> = 7.3246 (4) Å	<i>V</i> = 568.96 (5) Å ³
<i>c</i> = 12.6055 (7) Å	<i>Z</i> = 2
<i>D_x</i> = 1.261 Mg m ⁻³	Mo <i>K</i> α radiation, λ = 0.71073 Å
μ = 0.08 mm ⁻¹	<i>F</i> (000) = 228
Crystal sizes = 0.25 * 0.25 * 0.18 mm ³	Crystal: Prism, colourless
No. of reflections collected = 13216	
No. of independent reflections = 4864	No. of reflections with <i>I</i> > 2σ(<i>I</i>) = 3329
θ range for data collection: θ_{max} = 36.4°, θ_{min} = 1.6°	
Goodness-of-ft on <i>F</i> 2 = 1.04	
<i>R</i> indices [<i>I</i> > 2 <i>s</i> (<i>I</i>)]: <i>R</i> 1 = 0.051, <i>wR</i> 2 = 0.167	
(<i>D</i> / <i>s</i>) max < 0.001	(<i>Dr</i>) max = 0.28 eÅ ⁻³ (<i>Dr</i>)min = -0.23 eÅ ⁻³
Measurement: X8 Apex, Bruker CCD	Program system: Apex 2
Structure determination: WinGX (SHELXL and SHELXS)	

Ester (8b). Yield: 65%; mp: 185–187°C; IR (KBr, cm⁻¹): 1680 (CONH), 1720 (CO ester), 3035 (NH); ¹H NMR (CDCl₃): δ 1.40 (t, 3H, CH₃, *J* = 7.1 Hz), 2.29–2.44 (m, 3H), 2.83–2.90 (m, 1H), 4.38 (q, 2H, CH₂O, *J* = 7.1 Hz), 6.48 (d, 1H, *J* = 16.1 Hz), 6.81 (d, 1H, *J* = 16.1 Hz), 7.21–7.30 (m, 4H, ArH), 7.33–7.44 (m, 5H, ArH), 7.54 (s, 1H, NH); ¹³C NMR (CDCl₃): δ 14.2 (CH₃), 28.7 (CH₂), 29.4 (CH₂), 62.4 (CH₂O), 87.7 (C-8a), 118.1 (2CH), 127.1 (2CH), 128.5 (CH), 128.8 (2CH), 129.0 (CH), 129.8 (2CH), 134.1 (CH), 135.0 (C), 139.3 (C), 140.2 (C), 145.9 (C), 158.5 (CO), 174.1 (CO ester); HRMS (ESI-TOF) *m/z*: calculated for C₂₂H₂₁ClN₄O₃Na [M + Na]⁺: 447.11944 found: 447.11900.

2.11. 1-(4-Nitro-phenyl)-6-oxo-8a-styryl-1,5,6,7,8,8a-hexahydro-[1,2,4]triazolo[4,3-*b*]pyridazine-3-carboxylic Acid Ethyl Ester (8c). Yield: 49%; mp: 168–170°C; IR (KBr, cm⁻¹): 1530, 1320 (NO₂), 1670 (CONH), 1725 (CO ester), 3050 (NH); ¹H NMR (CDCl₃): δ 1.41 (t, 3H, CH₃, *J* = 7.2 Hz), 2.24–2.36 (m, 3H), 2.74–2.81 (m, 1H), 4.39 (q, 2H, CH₂O, *J* = 7.2 Hz), 6.22 (d, 1H, *J* = 16.3 Hz), 6.85 (d, 1H, *J* = 16.3 Hz), 7.32–7.39 (m, 6H, ArH), 7.71 (s, 1H, NH), 7.73–7.78 (m, 1H, ArH), 8.03–8.13 (m, 2H, ArH); ¹³C NMR (CDCl₃): δ 14.1 (CH₃), 29.1 (CH₂), 30.4 (CH₂), 62.5 (CH₂O), 86.8 (C-8a), 122.1 (2CH), 122.8 (CH), 126.4 (2CH), 126.9 (2CH), 128.9 (2CH), 129.1 (CH), 132.5 (CH), 134.8 (C), 140.1 (C), 142.2

FIGURE 1: ORTEP III diagram of **4a**. Compound showing the molecular numbering scheme. Displacement ellipsoids are drawn at 50% probability for all atoms, except for H, for which they have been set to be artificially small.

FIGURE 3: ORTEP III diagram of **5a**. Compound showing the molecular numbering scheme. Displacement ellipsoids are drawn at 50% probability for all atoms, except for H, for which they have been set to be artificially small.

FIGURE 2: Partial packing view showing the chain formed by the hydrogen bridge N-H...O.

(C), 146.4 (C), 157.9 (CO), 172.1 (CO ester); HRMS (ESI-TOF) m/z : calculated for $C_{22}H_{22}N_5O_5[M + H]^+$: 436.16155 found: 436.16116.

2.12. 1-(2-Methyl-3-nitro-phenyl)-6-oxo-8a-styryl-1,5,6,7,8,8a-hexahydro-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxylic Acid Ethyl Ester (**8d**). Yield: 51%; mp: 136–138°C; IR (KBr, cm^{-1}): 1545, 1310 (NO_2), 1670 (CONH), 1710 (CO ester), 3060 (NH); 1H NMR ($CDCl_3$): δ 1.40 (t, 3H, CH_3 , $J = 7.2$ Hz), 2.01–2.11 (m, 1H), 2.40 (s, 3H, CH_3), 2.45–2.64 (m, 3H), 4.40 (q, 2H, CH_2O , $J = 7.2$ Hz), 6.15 (d, 1H,

FIGURE 4: Partial packing view showing the chain formed by C-H...O.

$J = 16.0$ Hz), 6.86 (d, 1H, $J = 16.0$ Hz), 7.29–7.41 (m, 6H, ArH), 7.52 (d, 1H, $J = 8.1$ Hz), 7.76 (s, 1H, NH), 7.80 (d, 1H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 16.0 (CH_3), 28.6 (CH_2), 30.3 (CH_2), 62.6 (CH_2O), 88.9 (C-8a), 123.8 (CH), 126.2 (CH), 126.7 (CH), 127.0 (2CH), 128.9 (2CH), 129.1 (CH), 131.9 (C), 133.0 (CH), 133 (CH), 134.9 (C), 140.2 (C), 147.4 (C), 157.8 (CO), 171.9 (CO ester).

SCHEME 1

SCHEME 2

2.13. 1-(2,4-Dibromo-phenyl)-6-oxo-8a-styryl-1,5,6,7,8,8a-hexahydro-[1,2,4]triazolo[4,3-b]pyridazine-3-carboxylic Acid Ethyl Ester (**8e**). Yield: 46%; mp: 160–162°C; IR (KBr, cm⁻¹): 1675 (CONH), 1715 (CO ester), 3060 (NH); ¹H NMR (CDCl₃): δ 1.38 (t, 3H, CH₃, J = 7.1 Hz), 2.08–2.18 (m, 1H), 2.45–2.62 (m, 2H), 2.78–2.90 (m, 1H), 4.39 (q, 2H, CH₂O, J = 7.1 Hz), 6.20 (d, 1H, J = 15.9 Hz), 6.79 (d, 1H, J = 15.9 Hz), 7.14 (d, 1H, J = 8.5 Hz), 7.32–7.38 (m, 5H, ArH), 7.40 (dd, 1H, J = 8.1 and 2.2 Hz), 7.61 (s, 1H, NH), 7.80 (d, 1H, J = 2.2 Hz); ¹³C NMR (CDCl₃): δ 14.2 (CH₃), 28.9 (CH₂), 31.9 (CH₂), 62.5 (CH₂O), 88.0 (C-8a), 122.2 (C), 123.8 (C), 127.0 (2CH), 128.8 (2CH), 128.9 (CH), 131.1 (CH), 131.9 (CH), 133.0 (CH), 136.7 (CH), 138.5 (CH), 142.5 (C), 146.2 (C), 157.9 (CO), 173.1 (CO ester).

3. Results and Discussion

The starting compounds 6-(styryl)-4,5-dihydropyridazinones **4a**, **b** used for alkylation reaction and 1,3-dipolar cyclo-additions, were prepared from levulinic acid **1** according to Scheme 1. The treatment of compound **1** with the aromatic aldehydes **2a**, **b** produced the intermediate benzylidenelevulinic acid **3a**, **b**. The derivatives **3a**, **b** obtained were then treated with hydrazine hydrate in refluxing acetic acid in order to achieve the desired styrylpyridazinones **4a**, **b**.

The structure of compound **4a** was confirmed for the first time by X-ray crystallography (Figures 1 and 2 and

Table 1). The crystal structure of this compound, whose molecular formula is C₁₂H₁₂N₂O, was determined by single-crystal diffraction methods. The compound crystallizes in the monoclinic unit cell P2₁/n space group symmetry with lattice parameters: *a* = 8.0348(6) Å, *b* = 11.1532(6) Å, *c* = 11.9941(8) Å, and β = 101.074(2)°; *V* = 1054.82(12) Å³ and *D* (calc., *Z* = 4) = 1.261 Mg m⁻³. A total of 11692 data reflections were collected over the range of 5° ≤ 2θ ≤ 55°; of these, 1647 (independent and with I ≥ 2σ(I)) were used in the structural analysis. The final *R*(*F*) and *R*_w(*F*) residuals were 0.054 and 0.179, respectively.

In compound **4a**, the dihydropyridazinone ring is oriented at dihedral angles of 17.11 (9)° with respect to the benzene ring. In the crystal, the molecules are linked by N–H...O hydrogen bonds (Figure 2).

The *N*-alkylation reaction in the pyridazinone series is generally used for the introduction of pharmacophoric groups; consequently first of all it is necessary to study the alkylation reaction in the presence of 4,5-dihydropyridazinone and base in order to establish their reactivity and possible regioselectivity. The treatment of 6-styryl-4,5-dihydropyridazinone (**4a**) with alkyl halides (CH₃I, BrCH₂CH=CH₂ and BrCH₂COC₆H₅) in the presence of anhydrous K₂CO₃ in dry THF gave only the *N*-substituted-pyridazinones **5a–c** in moderate to good yields (Scheme 2).

The structures of *N*-substituted pyridazinones **5a–c** were characterized using ¹H NMR and ¹³C NMR spectra.

SCHEME 3

The exclusive alkylation at the 2-N position was confirmed by X-ray crystallography of compound **5a** (Figures 3 and 4 and Table 2). The crystal structure of compound **5a**, whose molecular formula is $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$, was also determined by single-crystal diffraction methods. The compound crystallizes in the monoclinic unit cell $P2_1$ space group symmetry with lattice parameters: $a = 6.1966(3) \text{ \AA}$, $b = 7.3246(4) \text{ \AA}$, $c = 12.6055(7) \text{ \AA}$, and $\beta = 96.035(4)^\circ$; $V = 568.96(5) \text{ \AA}^3$ and D (calc., $Z = 2$) = 1.261 Mg m^{-3} . A total of 13216 data were collected over the range of $3.2^\circ \leq 2\theta \leq 72.8^\circ$; of these, 3329 (independent and with $I \geq 2\sigma(I)$) were used in the structural analysis. The final $R(F)$ and $R_w(F)$ residuals were 0.051 and 0.167, respectively.

In compound **5a**, the dihydropyridazinone ring is oriented at dihedral angles of $20.96(8)^\circ$ with respect to the benzene ring. In the crystal, molecules are linked by C–H...O hydrogen bonds (Figure 4).

1,3-Dipolar cycloadditions offer a convenient one-step concerted route for the construction of five-membered heterocycles with multiple stereogenic centers [15–21]. In the present work, we report a full account on the examination on 1,3-dipolar cycloaddition reaction of 6-styryl-4,5-dihydropyridazinone **4a** with nitrile imines. The former compound has three potential dipolarophilic sites: the C=N double bond, the C=C double bond, and the C=O double bond. The reaction of compound **4a** with *N*-aryl-*C*-ethoxycarbonyl nitrile imines **7a–e**, generated *in situ* from ethyl hydrazono- α -bromoglyoxylates **6a–e** [22] and K_2CO_3 , was performed in refluxing dry THF. In all cases, only one type of triazolo[4,3-*b*]pyridazinone (**8a–e**) was obtained in moderate to good yields (Scheme 3). No adducts resulting from condensation on the double bonds C=C and/or C=O were detected. The reaction was exclusively site- and regioselective.

The structural assignments of the triazolo[4,3-*b*]pyridazinones **8a–e** are based on a full characterization by ^1H NMR and ^{13}C NMR spectra.

The ^1H NMR spectra of the compounds **8a–e**, show in particular the presence of two doublet signals at ranges

6.15–6.49 ppm and 6.79–6.86 ppm corresponding to the vinylic protons of the double bond HC=CH with a coupling constant of ca. 16.1–16.5 Hz; this excludes the addition of the dipole to the double bond HC=CH.

The ^{13}C NMR spectra of cycloadducts **8a–e**, exhibit a signal at 157.8–158.5 ppm assigned to the resonance of carbonyl carbon C=O; this excludes also the addition of the nitrile imine to the double bond C=O. These results demonstrate the site selectivity of the double bond C=N; the ^{13}C NMR spectra of cycloadducts **8a–e**, exhibit in each case a signal at 85.9–89.6 ppm due to the resonance of each quaternary carbon **C-8**. These carbon centres are then slightly deshielded. Such fact confirms the direction of the dipole addition to the C=N double bond; otherwise, the **C-8** signals would appear upfield (the value would be <60 ppm).

The reaction is thus regioselective and no 1,2,3-triazole is formed.

4. Conclusion

In summary, with a simple approach, a series of new *N*-substituted pyridazinones and triazolo[4,3-*b*]pyridazinones can be synthesized, from moderate to good yields, by reaction of 6-styryl-4,5-dihydro-2H-pyridazin-3-one **4a** with alkyl halides and using *N*-aryl-*C*-ethoxycarbonyl nitrile imines as 1,3-dipoles.

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References

- [1] S. Demirayak, A. C. Karaburun, and R. Beis, "Some pyrrole substituted aryl pyridazinone and phthalazinone derivatives and their antihypertensive activities," *European Journal of Medicinal Chemistry*, vol. 39, no. 12, pp. 1089–1095, 2004.
- [2] A. A. Siddiqui, R. Mishra, and M. Shaharyar, "Synthesis, characterization and antihypertensive activity of pyridazinone derivatives," *European Journal of Medicinal Chemistry*, vol. 45, no. 6, pp. 2283–2290, 2010.
- [3] Z. K. Sweeney, J. P. Dunn, Y. Li et al., "Discovery and optimization of pyridazinone non-nucleoside inhibitors of HIV-1 reverse transcriptase," *Bioorganic and Medicinal Chemistry Letters*, vol. 18, no. 15, pp. 4352–4354, 2008.
- [4] M. Sonmez, I. Borber, and E. Akbas, "Synthesis, antibacterial and antifungal activity of some new pyridazinone metal complexes," *European Journal of Medicinal Chemistry*, vol. 41, no. 1, pp. 101–105, 2006.
- [5] L. Costantino, G. Rastelli, G. Cignarella, and D. Barlocco, "Synthesis and aldose reductase inhibitory activity of a new series of benzo[h]cinnolinone derivatives," *Farmaco*, vol. 55, no. 8, pp. 544–552, 2000.
- [6] S. K. Kwon and A. Moon, "Synthesis of 3-alkylthio-6-allylthio-pyridazine derivatives and their antihepatocarcinoma activity," *Archives of Pharmacol Research*, vol. 28, no. 4, pp. 391–394, 2005.
- [7] R. R. Harris, L. Black, S. Surapaneni et al., "ABT-963 [2-(3,4-difluoro-phenyl)-4-(3-hydroxy-3-methyl-butoxy)-5-(4-methanesulfonyl-phenyl)-2H-pyridazin-3-one], a highly potent and selective disubstituted pyridazinone cyclooxygenase-2 inhibitor," *Journal of Pharmacology and Experimental Therapeutics*, vol. 311, no. 3, pp. 904–912, 2004.
- [8] W. Malinka, A. Redzicka, and O. Lozach, "New derivatives of pyrrolo[3,4-d]pyridazinone and their anticancer effects," *Farmaco*, vol. 59, no. 6, pp. 457–462, 2004.
- [9] N. F. Abd El-Ghaffar, M. K. Mohamed, M. S. Kadah, A. M. Radwan, G. H. Said, and S. N. Abd el Al, "Synthesis and antitumor activities of some new pyridazinones containing the 2-phenyl-1H-indolyl moiety," *Journal of Chemical and Pharmaceutical Research*, vol. 3, no. 3, pp. 248–259, 2011.
- [10] S. Mojahidi, E. M. Rakib, H. Sekkak et al., "Synthesis and in-vitro cytotoxic evaluation of novel pyridazin-4-one derivatives," *Archiv der Pharmazie*, vol. 343, no. 5, pp. 310–313, 2010.
- [11] H. Sekkak, S. Mojahidi, E. M. Rakib et al., "Synthesis and antiproliferative evaluation of spirothiadiazolopyridazine derivatives," *Letters in Drug Design and Discovery*, vol. 7, no. 10, pp. 743–746, 2010.
- [12] S. Abouricha, E. M. Rakib, N. Benchat, M. Alaoui, H. Allouchi, and B. El Bali, "Facile synthesis of new spirothiadiazolopyridazines by 1,3-dipolar cycloaddition," *Synthetic Communications*, vol. 35, no. 16, pp. 2213–2221, 2005.
- [13] S. H. Zaheer, I. K. Kacker, and N. S. Rao, "Über die Kondensation von Lavulinsäure mit aromatischen Aldehyden," *Chemische Berichte*, vol. 89, no. 2, pp. 351–354, 1956.
- [14] I. Sircar, R. P. Steffen, G. Bobowski et al., "Cardiotonic agents. 9. Synthesis and biological evaluation of a series of (E)-4,5-dihydro-6-[2-[4-(1H-imidazol-1-yl)phenyl]ethenyl]-3(2H)-pyridazinones: a novel class of compounds with positive inotropic, antithrombotic, and vasodilatory activities for the treatment of congestive heart failure," *Journal of Medicinal Chemistry*, vol. 32, no. 2, pp. 342–350, 1989.
- [15] R. Huisgen, "1,3-Dipolar cycloadditions. Past and future," *Angewandte Chemie*, vol. 2, no. 10, pp. 565–598, 1963.
- [16] R. Huisgen, "Kinetics and mechanism of 1,3-dipolar cycloadditions," *Angewandte Chemie*, vol. 2, no. 11, pp. 633–645, 1963.
- [17] A. Padwa, Ed., *1,3-Dipolar Cycloaddition Chemistry*, Wiley, New York, NY, USA, 1984.
- [18] K. V. Gothelf and K. A. Jorgensen, "Asymmetric 1,3-dipolar cycloaddition reactions," *Chemical Reviews*, vol. 98, no. 2, pp. 863–909, 1998.
- [19] A. Padwa and A. M. Schoffstall, in *Advances in Cycloaddition*, D. P. Curran, Ed., vol. 2, pp. 1–89, JAI, London, UK, 1990.
- [20] S. Kobayashi and K. A. Jorgensen, Eds., *Cycloaddition Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 2002.
- [21] A. Padwa, *Synthetic Applications of 1, 3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, John Wiley & Sons, 2002.
- [22] D. B. Sharp and C. S. Hamilton, "Derivatives of 1,2,4-triazole and of pyrazole," *Journal of the American Chemical Society*, vol. 68, no. 4, pp. 588–591, 1946.