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Research Article

Alkylation and 1,3-Dipolar Cycloaddition of 6-Styryl-4,5-dihydro-2*H*-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 ^{1}H, ^{13}C 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. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 and solution (unless otherwise specified) with TMS as an internal reference using a Bruker AC 300 (^{1}H) or 75 MHz (^{13}C) instruments. Chemical shifts are given in δ parts per million (ppm). Multiplicities of ^{13}C 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 SiO_2 (silica gel 60 Merck 0.063–0.200 mm). Thin-layer chromatography (TLC) was carried out on SiO_2 (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); ^{1}H NMR (DMSO-d_6): δ 2.42 (t, 2H, CH_2, J = 7.8 Hz), 2.78 (t, 2H, CH_2, 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); ^{13}C NMR (DMSO-d_6): 20.6 (CH_2), 26.3 (CH_2), 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); ^{1}H NMR (DMSO-d_6): δ 2.38 (t, 2H, CH_2, J = 7.6 Hz), 2.75 (t, 2H, CH_2, J = 7.6 Hz), 3.78 (s, 3H, CH_3O), 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); ^{13}C NMR (DMSO-d_6): 20.6 (CH_2), 26.4 (CH_2), 55.6 (CH_3O), 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 CH_2Cl_2 (50 mL), washed with water and brine, dried over $MgSO_4$ 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); ^{1}H NMR ($CDCl_3$): δ 2.53 (t, 2H, CH_2, J = 7.4 Hz), 2.79 (t, 2H, CH_2, J = 7.4 Hz), 3.45 (s, 3H, NCH_3), 6.84 (d, 1H, J = 16.5 Hz), 6.93 (d, 1H, J = 16.5 Hz), 7.24–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 21.2 (CH_2), 26.8 (CH_2), 36.6 (NCH_3), 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 $C_{13}H_{15}N_2O$ $[M + H]^+$: 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); ^{1}H NMR ($CDCl_3$): δ 2.57 (t, 2H, CH_2, J = 7.5 Hz), 2.81 (t, 2H, CH_2, J = 7.5 Hz), 4.41–4.44 (m, 2H, NCH_2), 5.18–5.26 (m, 2H, $=CH_2$), 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); ^{13}C NMR ($CDCl_3$): δ 21.1 (CH_2), 26.9 (CH_2), 50.9 (NCH_2), 117.0 ($=CH_2$), 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 $C_{15}H_{17}N_2O$ $[M + H]^+$: 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); ^{1}H NMR ($CDCl_3$): δ 2.67 (t, 2H, CH_2, J = 7.6 Hz), 2.91 (t, 2H, CH_2, J = 7.6 Hz), 5.25 (s, 2H, NCH_2), 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); ^{13}C NMR ($CDCl_3$): δ 21.2 (CH_2), 26.6 (CH_2), 55.2 (NCH_2), 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 $C_{20}H_{19}N_2O_2$ $[M + H]^+$: 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(2*H*)-one (**4a**) (1.0 g, 5 mmol) and ethyl hydrazono-α-bromoglyoxylate (**6a–e**)(5 mmol) in dry THF (50 mL), K_2CO_3 (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); ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3H, CH_3, J = 7.2 Hz), 2.28 (s, 3H, CH_3), 2.26–2.39 (m, 3H), 2.78–2.89 (m, 1H), 4.37 (q, 2H, CH_2O, 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); ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 20.7 (CH_3), 28.6 (CH_2), 29.5 (CH_2), 62.2 (CH_2O), 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 $C_{23}H_{25}N_4O_3$ $[M + H]^+$: 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: $C_{12}H_{12}N_2O$		
Formula weight: 200.24		
Crystal system: monoclinic		Space group (no): $P2_1/n$ (14)
a = 8.0348 (6) Å		β = 101.074 (2)°
b = 11.1532 (6) Å		V = 1911.5 (3) Å^3
c = 11.9941 (8) Å		Z = 4
D_x = 1.261 Mg m^{-3}		Mo $K\alpha$ radiation, λ = 0.71073 Å
μ = 0.08 mm^{-1}		F(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 $F2$ = 1.07		
R indices [I > 2s(I)]: $R1$ = 0.054, $wR2$ = 0.179		
(D/s)max = 0.000		(Dr)max = 0.527 eÅ^{-3} (Dr)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: $C_{13}H_{14}N_2O$		
Formula weight: 214.26		
Crystal system: monoclinic		Space group: $P2_1$
a = 6.1966 (3) Å		β = 96.035 (4)°
b = 7.3246 (4) Å		V = 568.96 (5) Å^3
c = 12.6055 (7) Å		Z = 2
D_x = 1.261 Mg m^{-3}		Mo $K\alpha$ radiation, λ = 0.71073 Å
μ = 0.08 mm^{-1}		F(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 >2σ(I) = 3329
θ range for data collection: θ_{max} = 36.4°, θ_{min} = 1.6°		
Goodness-of-ft on $F2$ = 1.04		
R indices [I > 2s(I)]: $R1$ = 0.051, $wR2$ = 0.167		
(D/s) max < 0.001		(Dr) max = 0.28 eÅ^{-3} (Dr)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); ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3H, CH_3, J = 7.1 Hz), 2.29–2.44 (m, 3H), 2.83–2.90 (m, 1H), 4.38 (q, 2H, CH_2O, 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); ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 28.7 (CH_2), 29.4 (CH_2), 62.4 (CH_2O), 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 $C_{22}H_{21}ClN_4O_3Na$ [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 (NO_2), 1670 (CONH), 1725 (CO ester), 3050 (NH); ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 3H, CH_3, J = 7.2 Hz), 2.24–2.36 (m, 3H), 2.74–2.81 (m, 1H), 4.39 (q, 2H, CH_2O, 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); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 29.1 (CH_2), 30.4 (CH_2), 62.5 (CH_2O), 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

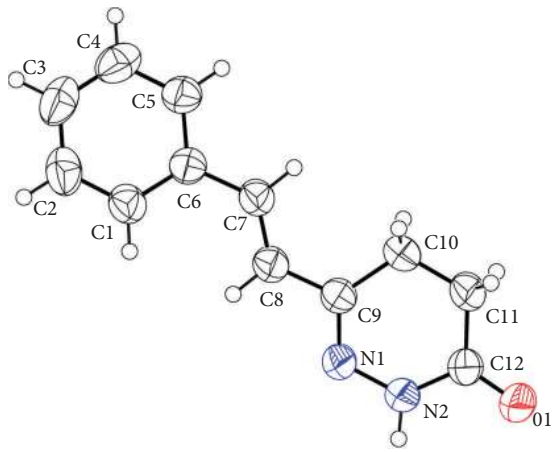


Figure 1: ORTEP III diagram of **4a**. Compound showing the molecular numbering scheme. Displacement ellipsoids are drawn at 50% probability for all atoms, except for H, for which they have been set to be artificially small.

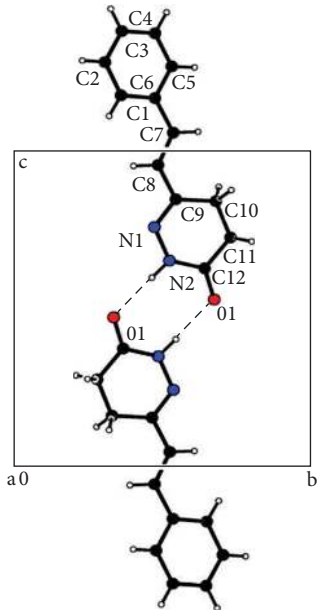


Figure 2: Partial packing view showing the chain formed by the hydrogen bridge N–H…O.

(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); ^{1}H 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,

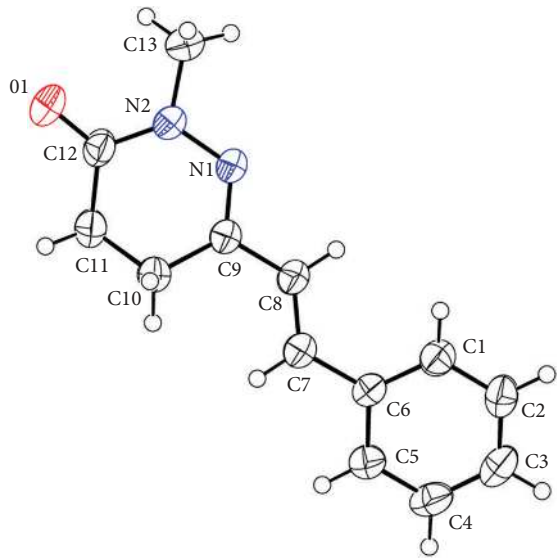


Figure 3: ORTEP III diagram of **5a**. Compound showing the molecular numbering scheme. Displacement ellipsoids are drawn at 50% probability for all atoms, except for H, for which they have been set to be artificially small.

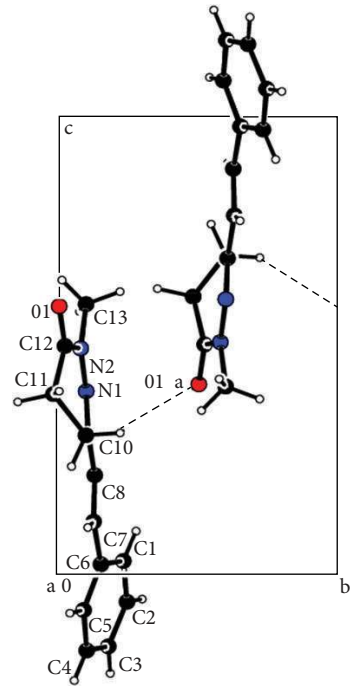
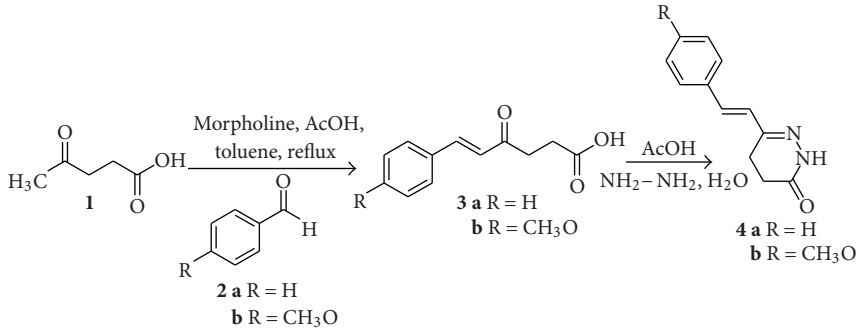
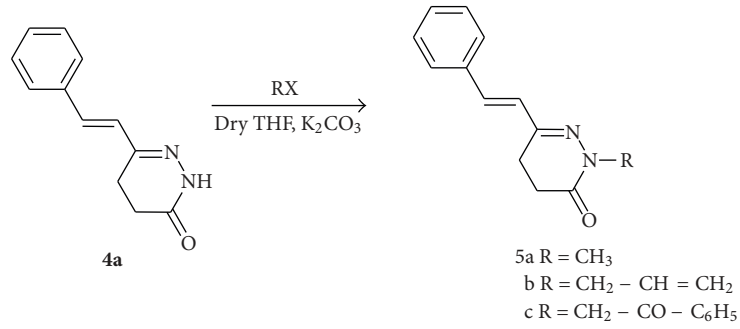


Figure 4: Partial packing view showing the chain formed by C–H…O.

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); ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, CH_3, 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, CH_2O, 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); ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 28.9 (CH_2), 31.9 (CH_2), 62.5 (CH_2O), 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

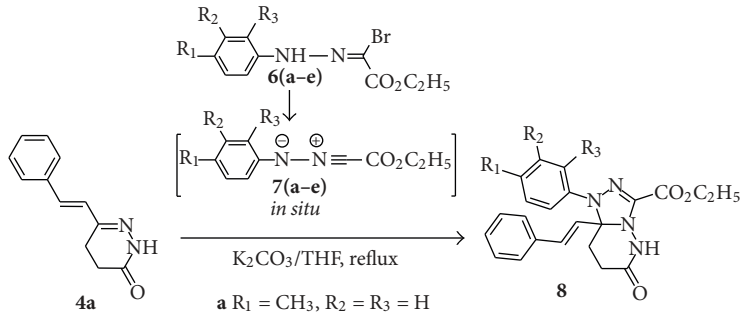
The starting compounds 6-(styryl)-4,5-dihydropyridazinones **4a**, **b** used for alkylation reaction and 1,3-dipolar cycloadditions, were prepared from levulinic acid **1** according to Scheme 1. The treatment of compound **1** with the aromatic aldehydes **2a**, **b** produced the intermediate benzylidenelevulinic 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 $C_{12}H_{12}N_2O$, was determined by single-crystal diffraction methods. The compound crystallizes in the monoclinic unit cell $P2_1/n$ 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) Å^3 and D (calc., Z = 4) = 1.261 Mg m^{-3}. A total of 11692 data reflections were collected over the range of $5° \leqslant 2\theta \leqslant 55°$; of these, 1647 (independent and with $I \geq 2\sigma(I)$) were used in the structural analysis. The final $R(F)$ and $R_w(F)$ residuals were 0.054 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 (CH_3I, $BrCH_2CH{=}CH_2$ and $BrCH_2COC_6H_5$) in the presence of anhydrous K_2CO_3 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 ^{1}H NMR and ^{13}C 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 $C_{13}H_{14}N_2O$, 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) Å, b = 7.3246(4) Å, c = 12.6055(7) Å, and β = 96.035(4)°; V = 568.96(5) Å^3 and D (calc., Z = 2) = 1.261 Mg m^{-3}. A total of 13216 data were collected over the range of 3.2° ≤ 2θ ≤ 72.8°; of these, 3329 (independent and with I ≥2σ(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)° 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 ^{1}H NMR and ^{13}C NMR spectra.

The ^{1}H 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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