A facile synthesis of new substituted spiropyrimidine-2,4-diones

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An efficient and short route to synthesise spiropyrimidine-2,4-diones was achieved using 1,3-dipolar cycloaddition followed by a cyclisation reaction. The reaction is regiospecific in all cases.

Keywords: spiropyrimidine-2,4-dione, 1,3-dipolar cycloaddition, cyclisation reaction, regiospecific reaction

Pyrimidine systems have attracted much attention owing to their wide range of biological activities, particularly in cancer research. Among these heterocycles, the pyridopyrimidine class is also of great interest because of its dihydrofolate reductase inhibiting, antibacterial,[1,2] antitumour[3] and antiepileptic activities.[4]

On the other hand, pyrimidine-2,4-diones are a class of bioactive heterocyclic molecules, the most famous examples being uracil and thymine, which form part of the nucleotides of RNA and DNA, respectively.[5] Pyrimidine-2,4-diones have attracted considerable attention in the pharmaceutical industry as anti-inflammatory agents,[6] dopamine receptor agonists,[7] serotonin uptake inhibitors[8] and antiepileptic agents.[9] A good example of a pyrimidine-2,4-dione derivative with a medicinal application is zidovudine (AZT, Fig. 1), used as an anti-AIDS agent.[10] This moiety is also the core structural element of some fungicides[11] and herbicides.[12]

1,3-Dipolar cycloaddition reactions are the most important and versatile methods to build five-membered heterocycles.[13–15] They have been applied to the synthesis of natural products such as sugar derivatives,[16] β-lactams,[17] amino acids[18] and alkaloids.[19]

We now report the synthesis of new spiropyrimidine-2,4-dione derivatives *via* 1,3-dipolar cycloaddition with nitrones in good yield.

Results and discussion

The synthesis of spiro-compound **5** commenced by the condensation reaction[20] of ethyl 2-(bromomethyl)acrylate **1** with primary amines. Three amines were selected for the formation of the ethyl 2-(aminomethyl)acrylate **2** in 50–73% yields. Compound **2** with isopropyl isocyanate were placed in anhydrous toluene.[21] The resulting mixture was stirred and heated to reflux under an argon atmosphere until complete consumption of the starting materials to furnish the product **3** in 65–80% yields. The next step in this synthesis was the formation of the isoxazolidine-core structures **4** by a 1,3-dipolar cycloaddition reaction[22] using three nitrones. This reaction is an important method for the formation of isoxazolidines[20] and has been used in the synthesis of natural products.[25,28] Two possible regioisomers of the cycloadducts can be theoretically obtained: the 5,5-disubstituted isoxazolidine and/or the 4,4-disubstituted isoxazolidines. In practice, we have obtained only one product. The structure of each cycloadduct was confirmed by NMR (^{1}H and ^{13}C) spectra of the crude cycloaddition reaction mixture. Comparison of the ^{13}C NMR data of adducts **4** suggests that these compounds possess the same regiochemistry. The chemical shift of carbon C_5 of the isoxazolidine ring of all adducts appears between 84 and 86 ppm. This value located the carbon C_5 near the very electronegative oxygen atom of the isoxazolidine ring.[23–25] Yields of **4** ranges between 62 and 77%. Finally, the synthesis of **5** could be achieved by the cyclisation of the ureido intermediate **4**. Compound **4** was dissolved in THF and a solution of *t*BuOK in THF (1 M) was added.[29–30] The reaction was stirred at room temperature for 1 h. The spiropyrimidine-2,4-dione 5 was obtained in good yield (Scheme 1, Table 1).

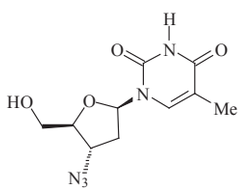
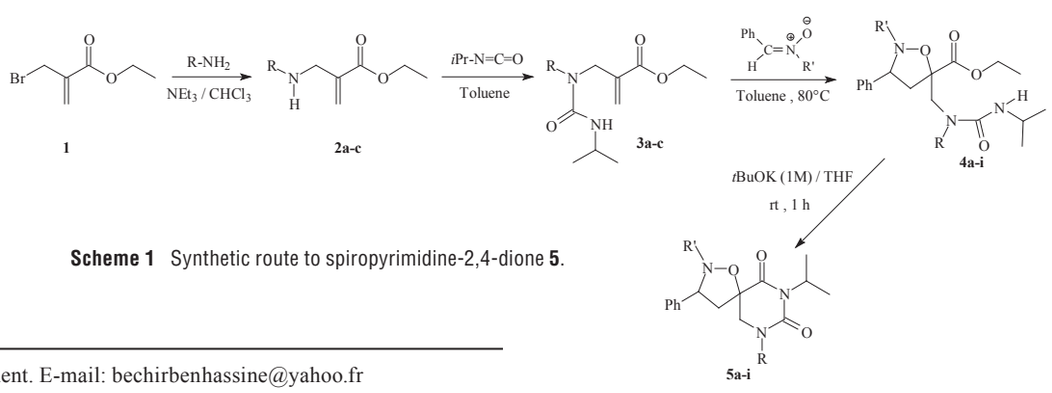


Fig. 1 Structure of zidovudine (AZT).

Table 1 Yields of adducts **4** and **5**

Entry	Amine R	Nitrone R'	Product	Yields/%	Product	Yields/%
1	Bn	Ph	**4a**	77	**5a**	84
2	Bn	*i*-Pr	**4b**	65	**5b**	75
3	Bn	*t*-Bu	**4c**	60	**5c**	79
4	*i*-Pr	Ph	**4d**	70	**5d**	72
5	*i*-Pr	*i*-Pr	**4e**	57	**5e**	82
6	*i*-Pr	*t*-Bu	**4f**	60	**5f**	70
7	*i*-Bu	Ph	**4g**	63	**5g**	80
8	*i*-Bu	*i*-Pr	**4h**	68	**5h**	75
9	*i*-Bu	*t*-Bu	**4i**	62	**5i**	78



Scheme 1 Synthetic route to spiropyrimidine-2,4-dione **5**.

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Conclusions

In summary, we have developed a facile route for the synthesis of new substituted spiropyrimidine-2,4-diones by a 1,3-dipolar cycloaddition reaction with nitrones, followed by cyclisation of a ureido intermediate. All spiroadducts were formed *via* a very high regioselectivity pathway, and the spirocarbon atom was linked to the isoxazolidine oxygen atom.

Experimental

All reactions were monitored by TLC Merck 60F-254 silica gel plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (70–230 mesh) using ethyl acetate and cyclohexane mixture as eluents. NMR spectra were recorded on a Bruker AC-300 spectrometer [300 MHz (^{1}H) and 75 MHz (^{13}C)]. All chemical shifts were reported as δ values (ppm) relative to internal tetramethylsilane. IR spectra (KBr) were recorded on a FTIR-8400 Shimadzu spectrophotometer. High resolution mass spectra (HR-MS) were obtained on a Waters Micromass Q-Tof Micro instrument.

Synthesis of compounds **3a–c;** *general procedure*

A solution of compound **2** (10 mmol) with isopropyl isocyanate (10 mmol) were placed in anhydrous toluene (10 mL). The resulting mixture was stirred and heated to reflux under an argon atmosphere until complete consumption of the starting materials (TLC analysis). The reaction mixture was allowed to cool to room temperature and concentrate. The residue obtained was purified by column chromatography [SiO_2/cyclohexane:ethyl acetate (90:10)] to furnish the products **3**.

Ethyl 2-{[benzyl(N-isopropylcarbamoyl)amino]methyl}acrylate (**3a**): Yellow liquid (80%); ^{1}H NMR (300 MHz, $CDCl_3$): 1.08 (d, $2CH_3$–*i*Pr), 1.16 (t, CH_3), 3.61 (m, CH–*i*Pr), 4.03 (q, CH_2), 4.26 (d, CH_2–Bn), 4.28 (d, CH_2–Bn),4.30 (s, NH), 4.34 (s, CH_2–N), 5.84 (d, CH=), 6.11 (d, CH=), 7.12–7.46 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.2 (CH_3), 22.5 ($2CH_3$–*i*Pr), 45.1 (CH–*i*Pr), 52.1 (CH_2–N), 52.3 (CH_2–Bn), 60.0 (CH_2–O), 122.1 (CH_2=), 126.4–135.4 (C_{arom}), 136.5 (C=), 159.9 (N–C=O), 172.0 (O–C=O); HRMS Calcd for $C_{17}H_{25}N_2O_3$ [M+H]$^+$: 305.1865; found: 305.1867.

Ethyl 2-{[isopropyl(N-isopropylcarbamoyl)amino]methyl}acrylate (**3b**): Yellow liquid (65%); ^{1}H NMR (300 MHz, $CDCl_3$): 1.07 (d, $2CH_3$–*i*Pr), 1.18 (t, CH_3), 1.22 (d, $2CH_3$–*i*Pr), 3.59 (m, CH–*i*Pr), 4.05 (q, CH_2), 4.13 (m, CH–*i*Pr), 4.13 (s, NH), 4.24 (s, CH_2–N), 5.75 (d, CH=), 6.37 (d, CH=); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.3 (CH_3), 19.9 ($2CH_3$–*i*Pr), 22.7 ($2CH_3$–*i*Pr), 45.7 (CH–*i*Pr), 48.6 (CH_2–N), 50.2 (CH–*i*Pr), 60.1 (CH_2–O), 118.8 (CH_2=), 138.1 (C=), 159.7 (N–C=O), 171.7 (O–C=O); HRMS Calcd for $C_{13}H_{25}N_2O_3$ [M+H]$^+$: 257.1865; found: 257.1866.

Ethyl 2-{[isobutyl(N-isopropylcarbamoyl)amino]methyl}acrylate (**3c**): Yellow liquid (72%); ^{1}H NMR (300 MHz, $CDCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): 0.84 (d, $2CH_3$–*i*Bu), 1.01 (m, CH–*i*Bu), 1.06 (d, $2CH_3$–*i*Pr), 1.16 (t, CH_3), 3.27 (m, CH_2–*i*Bu), 3.60 (m, CH–*i*Pr), 4.03 (q, CH_2), 4.30 (s, CH_2–N), 4.35 (s, NH), 5.82 (d, CH=), 6.05 (d, CH=); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.1 (CH_3), 20.1 ($2CH_3$–*i*Bu), 22.6 ($2CH_3$–*i*Pr), 26.6 (CH–*i*Bu), 45.2 (CH–*i*Pr), 51.7 (CH_2–N), 57.2 (CH_2–*i*Bu), 60.2 (CH_2–O), 122.1 (CH_2=), 137.1 (C=), 160.2 (N–C=O), 172.1 (O–C=O); HRMS Calcd for $C_{14}H_{27}N_2O_3$ [M+H]$^+$: 271.2022; found: 271.2023.

1,3-Dipolar cycloaddition reactions of **4a–i***; general procedure*

A solution of nitrone (1 mmol) and compound **3** (1 mmol) in toluene (3 mL) was stirred at 80°C under an argon atmosphere for 24 h. The solvent was then removed, and the residue was purified by column chromatography [SiO_2/cyclohexane:ethyl acetate (90:10)] to give the compounds **4**.

Ethyl 5-{[benzyl(N-isopropylcarbamoyl)amino]methyl}-2,3-diphenylisoxazolidine-5-carboxylate (**4a**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.06 (d, $2CH_3$–*i*Pr), 1.18 (t, CH_3), 1.85 (s, NH), 2.51 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 3.14 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.50 (d, CH_2–N), 3.71 (m, CH–*i*Pr), 4.14 (q, CH_2), 4.49 (d, CH_2–Bn), 4.53 (d, CH_2–Bn), 5.42 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 6.94–7.43 (m, $15H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 13.8 (CH_3), 23.0 ($2CH_3$–*i*Pr), 42.7 (C_4), 46.9 (CH–*i*Pr), 51.2 (C_7), 51.4 (C_6), 62.0 (CH_2), 69.8 (C_3), 86.2 (C_5), 116.4–150.2 (C_{arom}), 158.7 (N–C=O), 171.6 (O–C=O); HRMS Calcd for $C_{30}H_{36}N_3O_4$ [M+H]$^+$: 502.2706; found: 502.2707; IR (KBr) cm^{-1}: 1252, 1531, 1645, 1737, 2966, 3368.

Ethyl 5-{[benzyl(N-isopropylcarbamoyl)amino]methyl}-2-isopropyl-3-phenylisoxazolidine-5-carboxylate (**4b**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.04 (m, $2CH_3$–*i*Pr), 1.20 (t, CH_3), 1.84 (s, NH), 2.35 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.88 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 2.96 (m, CH–*i*Pr), 3.51 (d, CH_2–N), 3.74 (m, CH–*i*Pr), 4.03 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 4.16 (q, CH_2), 4.50 (d, CH_2–Bn), 4.53 (d, CH_2–Bn), 7.14–7.42 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.0 (CH_3), 19.1 ($2CH_3$–*i*Pr), 23.2 ($2CH_3$–*i*Pr), 43.1 (C_4), 43.6 (CH–*i*Pr), 51.2 (C_7), 55.8 (C_6), 60.5 (CH–*i*Pr), 61.4 (CH_2), 66.6 (C_3), 84.1 (C_5), 126.0–140.8 (C_{arom}), 159.5 (N–C=O), 171.0 (O–C=O); HRMS Calcd for $C_{27}H_{38}N_3O_4$ [M+H]$^+$: 468.2863; found: 468.2865; IR (KBr) cm^{-1} : 1256, 1535, 1647, 1740, 2970, 3369.

Ethyl 5-{[benzyl(N-isopropylcarbamoyl)amino]methyl}-2-tert-butyl-3-phenylisoxazolidine-5-carboxylate (**4c**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.08 (d, $2CH_3$–*i*Pr), 1.12 (s, $3CH_3$–*t*Bu), 1.22 (t, CH_3), 1.83 (s, NH), 2.34 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.93 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 2.96 (m, CH–*i*Pr), 3.55 (d, CH_2–N), 3.73 (m, CH–*i*Pr), 4.16 (q, CH_2), 4.50 (d, CH_2–Bn), 4.29 (d, CH_2–Bn), 4.54 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 7.12–7.43 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.0 (CH_3), 23.2 ($2CH_3$–*i*Pr), 26.2 ($3CH_3$–*t*Bu), 43.7 (C_4), 52.2 (C_7), 55.8 (C_6), 60.5 (CH–*i*Pr), 61.4 (CH_2), 61.8 (C–*t*Bu), 64.9 (C_3), 83.8 (C_5), 126.8–140.9 (C_{arom}), 159.5 (N–C=O), 168.4 (O–C=O); HRMS Calcd for $C_{28}H_{40}N_3O_4$ [M+H]$^+$: 482.3019; found: 482.3021; IR (KBr) cm^{-1} : 1255, 1532, 1649, 1739, 2969, 3368.

Ethyl 5-{[isopropyl(isopropylcarbamoyl)amino]methyl}-2,3-diphenylisoxazolidine-5-carboxylate (**4d**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (d, $2CH_3$–*i*Pr), 1.18 (d, $2CH_3$–*i*Pr), 1.20 (t, CH_3), 1.71 (s, NH), 2.22 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.83 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.42 (d, CH_2–N), 3.86 (m, CH–*i*Pr), 4.16 (q, CH_2), 4.26 (m, CH–*i*Pr), 4.89 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 6.74–7.52 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 13.8 (CH_3), 20.2 ($2CH_3$–*i*Pr), 23.3 ($2CH_3$–*i*Pr), 42.4 (CH–*i*Pr), 43.2 (C_4), 50.4 (CH–*i*Pr), 52.3 (C_6), 61.4 (CH_2), 69.9 (C_3), 86.4 (C_5), 115.8–150.0 (C_{arom}), 160.2 (N–C=O), 168.0 (O–C=O); HRMS Calcd for $C_{26}H_{36}N_3O_4$ [M+H]$^+$: 454.2706; found: 454.2709; IR (KBr) cm^{-1} : 1252, 1534, 1645, 1740, 2965, 3370.

Ethyl 5-{[isopropyl(isopropylcarbamoyl)amino]methyl}-2-isopropyl-3-phenylisoxazolidine-5-carboxylate (**4e**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.06 (m, $2CH_3$–*i*Pr), 1.13 (m, $2CH_3$–*i*Pr), 1.20 (m, $2CH_3$–*i*Pr), 1.24 (t, CH_3), 1.80 (s, NH), 2.06 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.62 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 2.90 (m, CH–*i*Pr), 3.51 (d, CH_2–N), 3.86 (m, CH–*i*Pr), 4.04 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 4.16 (q, CH_2), 4.28 (m, CH–*i*Pr), 7.27–7.37 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.0 (CH_3), 19.0 ($2CH_3$–*i*Pr), 20.3 ($2CH_3$–*i*Pr), 23.1 ($2CH_3$–*i*Pr), 42.4 (CH–*i*Pr), 43.3 (C_4), 52.4 (CH–*i*Pr), 52.3 (C_6), 60.5 (CH–*i*Pr), 61.4 (CH_2), 66.0 (C_3), 86.4 (C_5), 127.1–140.1 (C_{arom}), 160.2 (N–C=O), 169.0 (O–C=O); HRMS Calcd for $C_{23}H_{37}N_3O_4$ [M+H]$^+$: 420.2863; found: 420.2864; IR (KBr) cm^{-1} : 1253, 1534, 1646, 1739, 2968, 3369.

Ethyl 5-{[isopropyl[(isopropyl carbamoyl)amino]methyl}-2-tert-butyl-3-phenylisoxazolidine-5-carboxylate (**4f**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (s, $3CH_3$–*t*Bu), 1.15 (d, $2CH_3$–*i*Pr), 1.20 (d, $2CH_3$–*i*Pr), 1.24 (t, CH_3), 1.85 (s, NH), 2.08 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.63 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.54 (d, CH_2–N), 3.86 (m, CH–*i*Pr), 4.17 (q, CH_2), 4.29 (m, CH–*i*Pr), 4.57 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 7.28–7.34 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.1 (CH_3), 20.1 ($2CH_3$–*i*Pr), 23.4 ($2CH_3$–*i*Pr), 26.4 ($3CH_3$–*t*Bu), 42.4 (CH–*i*Pr), 43.9 (C_4), 50.5 (CH–*i*Pr), 52.3 (C_6), 61.6 (CH_2), 61.9 (C–*t*Bu), 65.0 (C_3), 86.1 (C_5), 126.9–140.1 (C_{arom}), 160.2 (N–C=O), 169.3 (O–C=O); HRMS Calcd for $C_{24}H_{40}N_3O_4$ [M+H]$^+$: 434.3019; found: 434.3022; IR (KBr) cm^{-1} : 1250, 1533, 1647, 1739, 2966, 3370.

Ethyl 5-{[isobutyl[(isopropyl carbamoyl)amino]methyl}-2,3-diphenylisoxazolidine-5-carboxylate (**4g**): Yellow liquid; ^{1}H NMR

(300 MHz, $CDCl_3$): 0.85 (d, $2CH_3$–*i*Bu), 1.07 (d, $2CH_3$–*i*Pr), 1.11 (m, CH-*i*Bu), 1.20 (t, CH_3), 1.68 (s, NH), 2.50 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 3.07 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.29 (d, CH_2–*i*Bu), 3.52 (d, CH_2–N), 3.74 (m, CH–*i*Pr), 4.15 (q, CH_2), 4.90 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 6.73–7.53 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 13.9 (CH_3), 20.1 ($2CH_3$–*i*Bu), 23.2 ($2CH_3$–*i*Pr), 26.3 (CH–*i*Bu), 43.0 (C_4), 43.6 (CH–*i*Pr), 50.4 (CH–*i*Pr), 55.4 (C_6), 57.1 (CH_2–*i*Bu), 61.6 (CH_2), 69.8 (C_3), 88.4 (C_5), 115.7–150.8 (C_{arom}), 159.8 (N–C=O), 169.1 (O–C=O); HRMS Calcd for $C_{27}H_{38}N_3O_4$ $[M+H]^+$: 468.2863; found: 468.2864; IR (KBr) cm^{-1} : 1250, 1532, 1648, 1738, 2969, 3368.

Ethyl 5-{[isobutyl[(isopropyl carbamoyl)amino]methyl}-2-isopropyl-3-phenylisoxazolidine-5-carboxylate (**4h**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 0.86 (d, $2CH_3$–*i*Bu), 1.08 (m, CH_3–*i*Pr), 1.12 (m, CH–*i*Bu), 1.21 (t, CH_3), 1.66 (s, NH), 2.35 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.89 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.30 (d, CH_2–*i*Bu), 3.54 (d, CH_2–N), 3.78 (m, CH–*i*Pr), 4.05 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 4.13 (q, CH_2), 7.29–7.35 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.1 (CH_3), 19.1 ($2CH_3$–*i*Pr), 20.2 ($2CH_3$–*i*Bu), 23.0 ($2CH_3$–*i*Pr), 26.5 (CH–*i*Bu), 43.2 (C_4), 43.6 (CH–*i*Pr), 55.4 (C_6), 57.2 (CH_2–*i*Bu), 60.6 (CH–*i*Pr), 61.3 (CH_2), 66.1 (C_3), 88.5 (C_5), 127.2–140.8 (C_{arom}), 159.8 (N–C=O), 169.5 (O–C=O); HRMS Calcd for $C_{24}H_{40}N_3O_4$ $[M+H]^+$: 434.3019; found: 434.3018; IR (KBr) cm^{-1} : 1251, 1532, 1649, 1740, 2969, 3369.

Ethyl 5-{[isobutyl[(isopropyl carbamoyl)amino]methyl}-2-tert-butyl-3-phenylisoxazolidine-5-carboxylate (**4i**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 0.84 (d, $2CH_3$–*i*Bu), 1.06 (d, $2CH_3$–*i*Pr), 1.11 (s, $3CH_3$–*t*Bu), 1.13 (m, CH–*i*Bu), 1.24 (t, CH_3), 1.70 (s, NH), 2.33 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.91 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.30 (d, CH_2–*i*Bu), 3.56 (d, CH_2–N), 3.73 (m, CH–*i*Pr), 4.17 (q, CH_2), 4.55 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 7.28–7.34 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.0 (CH_3), 20.2 ($2CH_3$–*i*Bu), 23.0 ($2CH_3$–*i*Pr), 26.2 ($3CH_3$–*t*Bu), 26.4 (CH–*i*Bu), 43.5 (CH–*i*Pr), 43.7 (C_4), 55.5 (C_6), 57.3 (CH_2–*i*Bu), 61.5 (CH_2), 65.0 (C_3), 88.2 (C_5), 126.8–140.9 (C_{arom}), 159.9 (N–C=O), 169.3 (O–C=O); HRMS Calcd for $C_{25}H_{42}N_3O_4$ $[M+H]^+$: 448.3176; found: 448.3179; IR (KBr) cm^{-1} : 1251, 1533, 1648, 1739, 2967, 3368.

*Cyclisation of spiropyrimidine-2,4-dione (**5a–l**); general procedure*

A solution of 1 M *t*BuOK in THF was added to a solution of intermediate **4** (0.10 mmol) in THF (3 mL). The reaction mixture was then stirred at room temperature for 1 h. A brine solution was added and the layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure.

9-Benzyl-7-isopropyl-2,3-diphenyl-1-oxa-2,7,9-triazaspiro[4.5]decane-6,8-dione (**5a**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.42 (d, $2CH_3$–*i*Pr), 2.57 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 3.12 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.75 (m, CH–*i*Pr), 3.86 (d, CH_2–N), 4.63 (d, CH_2–N), 4.66 (d, CH_2–Bn), 4.74 (d, CH_2–Bn), 4.72 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 6.93–7.69 (m, $15H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.9 ($2CH_3$–*i*Pr), 43.1 (C_4), 43.8 (CH–*i*Pr), 46.9 (C_6), 52.4 (C_7), 69.3 (C_3), 81.0 (C_5), 115.7–149.7 (C_{arom}), 155.1 (N–C=O), 170.0 (O–C=O); HRMS Calcd for $C_{28}H_{30}N_3O_3$ $[M+H]^+$: 456.2287; found: 456.2289; IR (KBr) cm^{-1} : 1166, 1334, 1340, 1639, 2980.

9-Benzyl-2,7-diisopropyl-3-phenyl-1-oxa-2,7,9-triazaspiro[4.5]decane-6,8-dione (**5b**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.06 (d, $2CH_3$–*i*Pr), 1.24 (d, $2CH_3$–*i*Pr), 2.42 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.78 (m, CH–*i*Pr), 2.95 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.75 (m, CH–*i*Pr), 3.84 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 3.87 (d, CH_2–N), 4.63 (d, CH_2–N), 4.66 (d, CH_2–Bn), 4.75 (d, CH_2–Bn), 7.09–7.51 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.1 ($2CH_3$–*i*Pr), 19.9 ($2CH_3$–*i*Pr), 43.2 (C_4), 43.9 (CH–*i*Pr), 49.9 (C_6), 52.5 (C_7), 60.1 (CH–*i*Pr), 65.3 (C_3), 81.1 (C_5), 126.9–139.5 (C_{arom}), 155.2 (N–C=O), 169.5 (O–C=O); HRMS Calcd for $C_{25}H_{32}N_3O_3$ $[M+H]^+$: 422.2444; found: 422.2446; IR (KBr) cm^{-1} : 1167, 1338, 1340, 1637, 2981.

9-Benzyl-2-tert-butyl-7-isopropyl-3-phenyl-1-oxa-2,7,9-triazaspiro[4.5]decane-6,8-dione (**5c**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.14 (s, $3CH_3$–*t*Bu), 1.25 (d, $2CH_3$–*i*Pr), 2.43 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.93 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.73 (m, CH–*i*Pr), 3.84 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 3.86 (d, CH_2–N), 4.64 (d, CH_2–N), 4.66 (d, CH_2–Bn), 4.75 (d, CH_2–Bn), 7.08–7.52 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.0 ($2CH_3$–*i*Pr), 26.4 ($3CH_3$–*t*Bu), 43.7 (C_4), 43.9 (CH–*i*Pr), 50.0 (C_6), 52.3 (C_7), 61.7 (C–*t*Bu), 64.2 (C_3), 80.8 (C_5), 126.6–139.9 (C_{arom}), 155.1 (N–C=O), 168.7 (O–C=O); HRMS Calcd for $C_{26}H_{34}N_3O_3$ $[M+H]^+$: 436.2600; found: 436.2601; IR (KBr) cm^{-1} : 1169, 1335, 1341, 1640, 2978.

7,9-Diisopropyl-2,3-diphenyl-1-oxa-2,7,9-triazaspiro[4.5]decane-6,8-dione (**5d**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (d, $2CH_3$–*i*Pr), 1.24 (d, $2CH_3$–*i*Pr), 2.29 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.81 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.47 (m, 2CH–*i*Pr), 3.64 (d, CH_2–N), 4.39 (d, CH_2–N), 4.75 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 6.92–7.68 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.9 ($2CH_3$–*i*Pr), 21.6 ($2CH_3$–*i*Pr), 43.2 (C_4), 44.8 (CH–*i*Pr), 47.0 (C_6), 47.8 (CH–*i*Pr), 69.2 (C_3), 83.4 (C_5), 115.6–149.0 (C_{arom}), 155.8 (N–C=O), 169.7 (O–C=O); HRMS Calcd for $C_{24}H_{30}N_3O_3$ $[M+H]^+$: 408.2287; found: 408.2290; IR (KBr) cm^{-1}: 1166, 1334, 1340, 1638, 2979.

2,7,9-Triisopropyl-3-phenyl-1-oxa-2,7,9-triazaspiro[4.5]decane-6,8-dione (**5e**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.06 (d, $2CH_3$–*i*Pr), 1.10 (d, $2CH_3$–*i*Pr), 1.24 (d, $2CH_3$–*i*Pr), 2.14 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.64 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 2.77 (m, CH–*i*Pr), 3.50 (m, 2CH–*i*Pr), 3.64 (d, CH_2–N), 3.87 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 4.38 (d, CH_2–N), 7.17–7.50 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.4 ($2CH_3$–*i*Pr), 19.8 ($2CH_3$–*i*Pr), 21.6 ($2CH_3$–*i*Pr), 43.4 (C_4), 44.9 (CH–*i*Pr), 46.5 (C_6), 47.8 (CH–*i*Pr), 60.1 (CH–*i*Pr), 65.4 (C_3), 83.4 (C_5), 127.0–139.2 (C_{arom}), 155.8 (N–C=O), 169.9 (O–C=O); HRMS Calcd for $C_{21}H_{32}N_3O_3$ $[M+H]^+$: 374.2444; found: 374.2446; IR (KBr) cm^{-1} : 1167, 1334, 1341, 1638, 2978.

2-Tert-butyl-7,9-diisopropyl-3-phenyl-1-oxa-2,7,9-triazaspiro[4.5]decane-6,8-dione (**5f**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 1.07 (d, $2CH_3$–*i*Pr), 1.13 (s, $3CH_3$–*t*Bu), 1.24 (d, $2CH_3$–*i*Pr), 2.15 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.66 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.47 (m, 2CH–*i*Pr), 3.64 (d, CH_2–N), 3.37 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 4.40 (d, CH_2–N), 7.17–7.46 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.8 ($2CH_3$–*i*Pr), 21.8 ($2CH_3$–*i*Pr), 26.3 ($3CH_3$–*t*Bu), 43.8 (C_4), 44.9 (CH–*i*Pr), 46.5 (C_6), 47.8 (CH–*i*Pr), 61.9 (C–*t*Bu), 64.4 (C_3), 83.1 (C_5), 126.5–139.2 (C_{arom}), 155.8 (N–C=O), 169.6 (O–C=O); HRMS Calcd for $C_{22}H_{34}N_3O_3$ $[M+H]^+$: 388.2600; found: 388.2602; IR (KBr) cm^{-1} : 1165, 1331, 1339, 1640, 2981.

9-Isobutyl-7-isopropyl-2,3-diphenyl-1-oxa-2,7,9-triazaspiro[4.5]decane-6,8-dione (**5g**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 0.90 (d, $2CH_3$–*i*Bu), 1.25 (d, $2CH_3$–*i*Pr), 1.30 (d, CH–*i*Bu), 2.59 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 3.10 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.41 (d, CH_2–*i*Bu), 3.73 (m, CH–*i*Pr), 3.78 (d, CH_2–N), 4.54 (d, CH_2–N), 4.76 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 6.93–7.69 (m, $10H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.8 ($2CH_3$–*i*Bu), 19.9 ($2CH_3$–*i*Pr), 26.5 (CH–*i*Bu), 43.1 (C_4), 43.8 (CH–*i*Pr), 50.0 (C_6), 61.3 (CH_2–*i*Bu), 69.3 (C_3), 85.4 (C_5), 115.7–149.7 (C_{arom}), 155.4 (N–C=O), 168.9 (O–C=O); HRMS Calcd for $C_{25}H_{32}N_3O_3$ $[M+H]^+$: 422.2444; found: 422.2445; IR (KBr) cm^{-1} : 1166, 1335, 1336, 1639, 2980.

9-Isobutyl-2,7-diisopropyl-3-phenyl-1-oxa-2,7,9-triazaspiro[4.5]decane-6,8-dione (**5h**): Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 0.90 (d, $2CH_3$–*i*Bu), 1.07 (d, $2CH_3$–*i*Pr), 1.26 (d, $2CH_3$–*i*Pr), 1.31 (d, CH–*i*Bu), 2.42 (dd, H_{4a}, J = 12.9 Hz, J = 9.6 Hz), 2.77 (m, CH–*i*Pr), 2.92 (d, H_{4b}, J = 12.9 Hz, J = 7.5 Hz), 3.40 (d, CH_2–*i*Bu), 3.75 (m, CH–*i*Pr), 3.80 (d, CH_2–N), 3.88 (dd, H_3, J = 9.6 Hz, J = 7.5 Hz), 4.56 (d, CH_2–N), 7.17–7.52 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.1 ($2CH_3$–*i*Pr), 19.9 ($2CH_3$–*i*Bu), 20.1 ($2CH_3$–*i*Pr), 26.7 (CH–*i*Bu), 43.2 (C_4), 43.9 (CH–*i*Pr), 50.1 (C_6), 60.2 (CH–*i*Pr), 61.4 (CH_2–*i*Bu), 69.4 (C_3), 85.4 (C_5), 126.8–139.9 (C_{arom}), 155.3 (N–C=O), 168.8 (O–C=O); HRMS Calcd for $C_{22}H_{34}N_3O_3$ $[M+H]^+$: 388.2600; found: 388.2602; IR (KBr) cm^{-1} : 1165, 1333, 1341, 1638, 2977.

2-tert-Butyl-9-isobutyl-7-isopropyl-3-phenyl-1-oxa-2,7,9-triazaspiro[4.5]decane-6,8-dione (**5i**): Yellow liquid; ^{1}H NMR

(300 MHz, $CDCl_3$): 0.89 (d, $2CH_3$–*i*Bu), 1.12 (s, $3CH_3$–*t*Bu), 1.23 (d, $2CH_3$–*i*Pr), 1.28 (d, CH–*i*Bu), 2.44 (dd, H_{4a}, $J = 12.9$ Hz, $J = 9.6$ Hz), 2.90 (d, H_{4b}, $J = 12.9$ Hz, $J = 7.5$ Hz), 3.39(d, CH_2–*i*Bu), 3.72 (m, CH–*i*Pr), 3.80 (d, CH_2–N), 4.38 (dd, H_3, $J = 9.6$ Hz, $J = 7.5$ Hz), 4.56 (d, CH_2–N), 7.16–7.46 (m, $5H_{arom}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.9 ($2CH_3$–*i*Pr), 26.5 ($3CH_3$–*t*Bu), 27.0 (CH–*i*Bu), 43.8 (C_4), 44.1 (CH–*i*Pr), 49.5 (C_6), 61.3 (CH_2–*i*Bu), 61.8 (C–*t*Bu), 64.3 (C_3), 85.2 (C_5), 126.5–140.0 (C_{arom}), 155.3 (N–C=O), 168.9 (O–C=O); HRMS Calcd for $C_{23}H_{36}N_3O_3$ $[M+H]^+$: 402.2757; found: 402.2759; IR (KBr) cm^{-1} : 1164, 1335, 1340, 1638, 2980.

The authors are grateful to DGRSRT (Direction Générale de la Recherche Scientifique et de la Rénovation Technologique) of the Tunisian Ministry of Higher Education, Scientific Research, and Technology for the financial support.

Received 12 May 2013; accepted 10 July 2013
Paper 1301944 doi: 10.3184/174751913X13783169779948
Published online: 7 October 2013

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