MRC Letters

Magnetic Resonance in Chemistry

Received: 6 December 2010 Revised: 17 February 2011 Accepted: 17 February 2011 Published online in Wiley Online Library: 31 March 2011

(wileyonlinelibrary.com) DOI 10.1002/mrc.2755

Synthesis and complete assignment of the ^{1}H and ^{13}C NMR spectra of 6-substituted and 2,6-disubstituted pyridazin-3(2*H*)-ones

Pedro Besada,* Tamara Costas, Noemi Vila, Carla Chessa and Carmen Terán

Several pyridazin-3(2*H*)-one derivatives were synthesized starting from alkyl furans using oxidation with singlet oxygen to give 4-methoxy or 4-hydroxybutenolides, key intermediates of the synthetic strategy followed. For all pyridazinones reported, a complete assignment of the ^{1}H and ^{13}C NMR spectra using one- and two-dimensional NMR spectroscopic methods, which included NOE, DEPT, COSY, HSQC and HMBC experiments, was accomplished. Correlations between the chemical shifts of the heterocyclic ring atoms and substituents at N-2 and C-6 were analyzed.

Keywords: ^{1}H NMR; ^{13}C NMR; NOE; COSY; HSQC; HMBC; pyridazinones

Introduction

Pyridazinones are useful scaffolds for building a broad range of chemicals.[1] Thus, polyfunctionalized pyridazin-3(2*H*)-ones are used as synthetic intermediates of different pyridazine analogues[1b] and pyridazino-fused ring systems.[2] Moreover, pyridazinone derivatives show important pharmacological properties,[3] particularly on cardiovascular system.[4] The 6-arylpyridazin-3(2*H*)-one structure was considered essential for the cardiovascular effects, especially to ensure inhibition of some key targets as phosphodiesterase III.[5] However, in recent years, new biologically active derivatives have been described, in which the aryl group at C-6 was removed or replaced, such as α_1-adrenoreceptor antagonists,[6] antiplatelet[7] and anti-inflammatory agents[8] or inhibitors of HIV-1 reverse transcriptase.[9]

Taking into account the interest of pyridazin-3(2*H*)-ones, both synthesis and full structural elucidation of new derivatives would be very useful for further research in this area. Thus, several interesting systematic studies for assignment of ^{1}H and ^{13}C chemical shifts in this class of heterocycles have been previously described, being most of them focused on pyridazine derivatives and pyridazino-fused systems.[10]

In this work, we describe the preparation of a series of biologically actives 6-substituted and 2,6-disubstituted pyridazin-3(2*H*)-ones (Fig. 1),[11] as well as a complete ^{1}H and ^{13}C NMR analysis, correlating the chemical shifts of pyridazinone ring atoms with the substituents at N-2 and C-6.

Results and Discussion

The pyridazin-3(2*H*)-ones studied (**3**–**8**) were obtained in moderate yields as outlined in Scheme 1.[11] Thus, pyridazinone nucleus was built starting from accessible alkyl furans, using oxidation with singlet oxygen to give 4-methoxy or 4-hydroxybutenolides. Both intermediates of this synthetic strategy are suitable for reaction with hydrazine or methyl hydrazine. Finally, standard procedures were applied to transform the unsubstituted NH analogues into *N*-benzyl derivatives as well as the silyl ethers into the corresponding alcohols.

^{1}H and ^{13}C NMR data (chemical shifts and coupling constants) for compounds **3**–**8** are shown in Tables 1 and 2 and the numbering of atoms is indicated in Fig. 1. Unambiguous assignments for all protons and carbons were made through the combined information of one-dimensional (1D) and two-dimensional (2D) NMR experiments [NOE, DEPT, COSY, HSQC and HMBC].

An assignment of the substituent alkyl protons on C-6 and N-2 was achieved considering chemical shift and multiplicity, allowing the assignment by direct correlation (HSQC) of carbons to which they are directly attached. However, COSY and HSQC experiments were performed to establish assignment of substituent aromatic protons for the different derivatives. Thus, on the basis of COSY and HSQC spectra, the chemical shifts of ^{1}H and ^{13}C nuclei of aromatic systems of *tert*-butyldiphenyl and benzyl groups (compounds **3**–**5** and **8**) were clearly assigned, even in spite of some ^{1}H signal overlap observed which exhibit a specific complex aromatic region in the case of 2-*N*-benzyl-6-*tert*-butyldiphenylsilyloxyalkyl derivatives (**5**, Table 1).

Pyridazine ring protons were assigned according to the chemical shift and multiplicity data and through sequential analysis of the NOE and COSY experiments. H-4 and H-5 chemical shifts range between δ = 6.82 and 7.58 ppm (Table 1). Both protons are easily defined considering the NOE effects displayed between H-1′ and H-5 (Fig. 2), and as it would be expected, H-5 is always the least shielded proton. For compounds **4a** and **5a**, H-5 appears overlapped with substituent aromatic protons on

* *Correspondence to: Pedro Besada, Departamento de Química Orgánica, Facultade de Química, Universidade de Vigo, 36310 Vigo, Spain.*
E-mail: pbes@uvigo.es

Departamento de Química Orgánica, Facultade de Química, Universidade de Vigo, 36310 Vigo, Spain

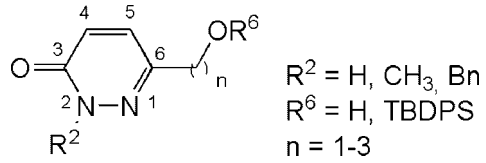
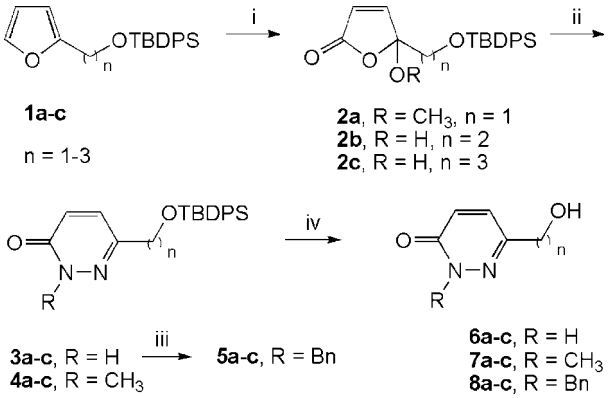


Figure 1. Pyridazin-3(2*H*)-one derivatives synthesized.

N-2 and/or C-6. However, a careful study on their COSY and HSQC spectra also allowed the precise identification of H-5. Moreover, it is noteworthy that for all compounds, H-4 and H-5 chemical shifts are practically not affected by the substitution at N-2. Very small shifts towards higher fields, not higher than 0.1 ppm, were detected for H-4 and H-5 when a methyl or a benzyl group is attached to N-2. In particular, the low variability of H-4 resonance suggests that compounds **3** and **6** exist exclusively as NH tautomers.[12] Nevertheless, more significant variations were found in the chemical shifts of the pyridazine ring protons depending on the alkyl chain length at C6, particularly for H-5. Thus, for the 6-silyloxyalkylpyridazinone derivatives, H-5 of the methylene derivatives (**3a**–**5a**) are 0.30 ± 0.01 ppm less shielded than those of the ethylene derivatives (**3b**–**5b**) and 0.38 ± 0.03 ppm less shielded than those of trimethylene derivatives (**3c**–**5c**). For the 6-hydroxyalkylpyridazinone derivatives, a similar but less intense effect was observed, with H-5 δ values for the methylene derivatives (**6a**–**8a**) of 0.16 ± 0.03 ppm at higher frequencies than for ethylene derivatives (**6b**–**8b**) and trimethylene derivatives (**6c**–**8c**). In contrast, the effect of the replacement of *tert*-



Scheme 1. Reagents and conditions: (i) (1) O_2, *hυ*, rose Bengal, MeOH, −78 °C, (2) Ac_2O, Py, DMAP, rt for **2a**; or O_2, *hυ*, rose Bengal, DIPEA, MeOH, −78 °C for **2b**–**c**; (ii) $NH_2NH_2{\cdot}H_2O$ or CH_3NHNH_2, EtOH, reflux or 0 °C; (iii) NaH, BnBr, Bu_4NI, THF, rt; (iv) TBAF, THF, rt.

Table 1. ^{1}H chemical shifts (δ in ppm) and coupling constants (*J* in Hz) for compounds **3**–**8**[a,b]

Compound	H-4	H-5	H-1′	H-2′	H-3′	R^2	R^6
3a	6.97 (d, 9.7)	7.50 (d, 9.7)	4.60 (s)			10.10 (br s, NH)	7.65 (*o*-H), 7.43 (*p*-H),[c] 7.38 (*m*-H),[c] 1.08 (s, CH_3)
3b	6.84 (d, 9.7)	7.18 (d, 9.7)	2.79 (t, 6.1)	3.92 (t, 6.1)		10.68 (br s, NH)	7.58 (*o*-H), 7.42 (*p*-H), 7.36 (*m*-H), 1.00 (s, CH_3)
3c	6.92 (d, 9.6)	7.14 (d, 9.6)	2.75 (t, 7.6)	1.92	3.74 (t, 6.0)	12.14 (br s, NH)	7.68 (*o*-H), 7.41 (*p*-H),[c] 7.36 (*m*-H),[c] 1.01 (s, CH_3)
4a	6.92 (d, 9.5)	7.43[c]	4.58 (s)			3.66 (s, CH_3)	7.64 (*o*-H), 7.44 (*p*-H),[c] 7.38 (*m*-H),[c] 1.07 (s, CH_3)
4b	6.82 (d, 9.4)	7.13 (d, 9.4)	2.77 (t, 6.0)	3.90 (t, 6.0)		3.71 (s, CH_3)	7.58 (*o*-H), 7.42 (*p*-H), 7.36 (*m*-H), 1.02 (s, CH_3)
4c	6.87 (d, 9.4)	7.07 (d, 9.4)	2.71 (t, 7.6)	1.89	3.71 (t, 6.1)	3.73 (s, CH_3)	7.66 (*o*-H), 7.43 (*p*-H),[c] 7.38 (*m*-H),[c] 1.06 (s, CH_3)
5a	6.93 (d, 9.6)	7.40 (d, 9.6)[c]	4.59 (s)			7.36 (*o*-H),[c] 7.29 (*m*-H, *p*-H), 5.22 (s, CH_2N),	7.63 (*o*-H), 7.43 (*p*-H),[c] 7.37 (*m*-H),[c] 1.07 (s, CH_3)
5b	6.83 (d, 9.5)	7.11 (d, 9.5)	2.79 (t, 6.4)	3.92 (t, 6.4)		7.39 (*o*-H),[c] 7.28 (*m*-H, *p*-H), 5.26 (s, CH_2N)	7.58 (*o*-H), 7.43 (*p*-H),[c] 7.35 (*m*-H),[c] 0.99 (s, CH_3)
5c	6.82 (d, 9.5)	6.99 (d, 9.5)	2.68 (t, 7.6)	1.87	3.70 (t, 6.0)	7.38 (*o*-H),[c] 7.26 (*m*-H, *p*-H), 5.24 (s, CH_2N)	7.63 (*o*-H), 7.42 (*p*-H),[c] 7.36 (*m*-H),[c] 1.05 (s, CH_3)
6a	6.98 (d, 9.7)	7.58 (d, 9.7)	4.47 (s)				
6b	6.91 (d, 9.6)	7.45 (d, 9.6)	2.81 (t, 6.4)	3.84 (t, 6.4)			
6c	6.93 (d, 9.8)	7.45 (d, 9.8)	2.72 (t, 7.7)	1.88	3.62 (t, 6.3)		
7a	6.97 (d, 9.5)	7.55 (d, 9.5)	4.47 (s)			3.73 (s, CH_3)	
7b	6.91 (d, 9.4)	7.42 (d, 9.4)	2.81 (t, 6.3)	3.84 (t, 6.3)		3.74 (s, CH_3)	
7c	6.90 (d, 9.6)	7.39 (d, 9.6)	2.70 (t, 7.7)	1.86	3.60 (t, 6.4)	3.72 (s, CH_3)	
8a	6.94 (d, 9.5)	7.23 (d, 9.5)	4.56 (s)			7.40 (*o*-H), 7.31 (*m*-H, *p*-H), 5.29 (s, CH_2N)	2.58 (br s, OH)
8b	6.92 (d, 9.6)	7.11 (d, 9.6)	2.84 (t, 5.8)	3.96 (t, 5.8)		7.42 (*o*-H), 7.34 (*m*-H, *p*-H), 5.31 (s, CH_2N)	2.34 (br s, OH)
8c	6.87 (d, 9.5)	7.07 (d, 9.5)	2.70 (t, 7.4)	1.90	3.66 (t, 6.2)	7.41 (*o*-H), 7.30 (*m*-H, *p*-H), 5.28 (s, CH_2N)	2.18 (br s, OH)

[a] If not specified otherwise, chemical shifts were measured in $CDCl_3$ solution. Multiplicity and coupling constants are given in parentheses. Multiplicity is not specified for signals that appear as multiplet.
[b] Compounds **6a**–**c** and **7a**–**c** were measured in CD_3OD solution.
[c] Overlapped signals; assigned based on the HSQC and/or COSY spectra.

Table 2. ^{13}C chemical shifts (δ in ppm) for compounds **3–8**[a,b]

Compound	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	R^2	R^6
3a	161.5	130.4	132.4	147.7	64.2				135.5 (*o*-CH), 132.6 (C), 130.0 (*p*-CH), 127.9 (*m*-CH), 26.8 (CH_3), 19.2 (CCH_3)
3b	160.9	129.6	134.9	147.0	37.5	62.6			135.5 (*o*-CH), 133.2 (C), 129.8 (*p*-CH), 127.7 (*m*-CH), 26.8 (CH_3), 19.1 (CCH_3)
3c	161.8	129.8	134.2	148.7	30.7	30.8	62.6		135.5 (*o*-CH), 133.6 (C), 129.6 (*p*-CH), 127.6 (*m*-CH), 26.8 (CH_3), 19.2 (CCH_3)
4a	160.4	129.7	131.0	146.4	64.4			39.9 (CH_3)	135.5 (*o*-CH), 132.7 (C), 130.0 (*p*-CH), 127.8 (*m*-CH), 26.8 (CH_3), 19.2 (CCH_3)
4b	160.3	128.9	133.6	146.0	37.6	62.7		40.1 (CH_3)	135.5 (*o*-CH), 133.1 (C), 129.8 (*p*-CH), 127.7 (*m*-CH), 26.7 (CH_3), 19.1 (CCH_3)
4c	160.2	129.4	132.7	147.6	30.9	31.0	62.6	40.0 (CH_3)	135.5 (*o*-CH), 133.7 (C), 129.6 (*p*-CH), 127.6 (*m*-CH), 26.8 (CH_3), 19.2 (CCH_3)
5a	159.9	130.3	130.8	146.7	64.4			136.2 (C), 128.6 (CH), 128.5 (CH), 127.7 (CH), 55.1 (CH_2N)	135.5 (*o*-CH), 132.7 (C), 130.0 (*p*-CH), 127.8 (*m*-CH), 26.8 (CH_3), 19.2 (CCH_3)
5b	159.8	129.5	133.4	146.1	37.7	62.7		136.4 (C), 128.6 (CH), 128.5 (CH), 127.7 (CH), 55.1 (CH_2N)	135.5 (*o*-CH), 133.2 (C), 129.8 (*p*-CH), 127.7 (*m*-CH) 26.7 (CH_3), 19.1 (CCH_3)
5c	159.7	130.1	132.6	147.6	30.9	30.8	62.6	136.5 (C), 128.6 (CH), 128.5 (CH), 127.7 (CH), 55.1 (CH_2N),	135.5 (*o*-CH, 133.7 (C), 129.7 (*p*-CH), 127.6 (*m*-CH), 26.9 (CH_3), 19.2 (CCH_3)
6a	163.7	130.8	134.6	150.2	63.5				
6b	163.6	130.3	136.6	149.1	38.4	61.3			
6c	163.5	130.5	136.3	150.9	31.7	32.1	62.0		
7a	162.6	130.3	133.5	149.8	63.5			40.6 (CH_3)	
7b	162.5	129.7	135.5	148.8	38.5	61.3		40.7 (CH_3)	
7c	162.3	130.0	135.2	150.5	31.9	32.2	62.0	40.6 (CH_3)	
8a	159.9	130.6	130.7	146.1	62.9			136.1 (C), 128.7 (CH), 128.6 (CH), 128.0 (CH), 55.1 (CH_2N)	
8b	159.6	130.5	133.0	146.1	36.8	60.4		136.3 (C), 128.7 (2CH), 128.0 (CH), 54.9 (CH_2N)	
8c	159.7	130.3	132.7	147.5	30.9	30.6	61.6	136.4 (C), 128.6 (CH), 128.5 (CH), 127.8 (CH), 55.0 (CH_2N)	

[a] If not specified otherwise, chemical shifts were measured in $CDCl_3$ solution.
[b] Compounds **6a–c** and **7a–c** were measured in CD_3OD solution.

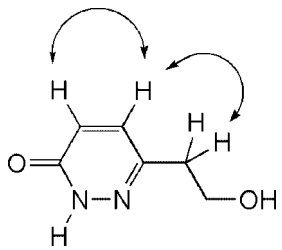


Figure 2. NOE correlations for compound **6b**.

butyldiphenylsilyloxy group by a hydroxyl group is appreciable only on H-5 for the methylene analogue **8a**, the shielding is 0.17 ppm larger than for **5a**.

The signals of the pyridazine ring carbons in compounds **3–8** are shown in Table 2. The quaternary carbons (C-3 and C-6) were assigned by the sequential analysis of HMBC experiments. C-3 resonances occur in the range δ = 159.6–161.5 ppm (measured in $CDCl_3$) or in the range δ = 162.3–163.7 ppm (measured in CD_3OD). The *N*-substitution, regardless of the nature of the substituent, shifts the C-3 signals to lower frequencies in different magnitudes; the effect of the substitution by a benzyl is slightly more intense than that of a methyl group. Thus, C-3 is shifted by 0.9 ± 0.3 ppm by the *N*-methyl and by 1.6 ± 0.6 ppm by the *N*-benzyl group. However, C-3 chemical shift differences observed are lower than they would be expected if the *N*-unsubstituted analogues were found predominantly in the hydroxyl form. For all analyzed compounds, the C-3 resonance was typical of a carbonyl group of a pyridazin-3-one nucleus[13] indicating that compounds **3** and **6** are also in the keto form. Additionally, the effect of the *N*-substitution on the C-6 chemical shift is similar for methyl and benzyl, both groups shield C-6; its signal is more intense in the silyl ether derivatives (1.0 ± 0.3 ppm). Moreover, the chemical

shift of C-6 is affected by the magnitude of the alkyl chain at this position. Thus, the C-6 resonance for the methylene derivatives was 0.7 ± 0.3 ppm less shielded than for ethylene derivatives but 1.0 ± 0.3 ppm more shielded than for trimethylene derivatives. Regarding the C-4 and C-5 signals, C-4 is more shielded than C-5 for all compounds studied showing a similar behavior to that found for H-4 and H-5. In addition, it is noteworthy that the C-5 resonance is the most affected by both N-2 and C-6 substitution. In particular, the inclusion of a methyl or a benzyl group at N-2 shifts C-5 signals by 1.3 ± 0.3 ppm to lower frequencies, while the increase in the alkyl chain length at C-6 shifts the same carbon signal 2.1 ± 0.4 ppm to higher frequencies. Finally, replacement of *tert*-butyldiphenylsilyloxy group by a hydroxyl group has no major effect on C-5, even for the methylene derivatives.

In conclusion, two series of pyridazin-3(2*H*)-ones, 6-substituted and 2,6-disubstituted, were synthesized in moderate yield starting from easily accessible alkyl furans. For all pyridazinone derivatives described, a complete assignment of all hydrogen and carbon NMR signals, using 1D and 2D NMR spectroscopic methods, was accomplished. The ^{1}H and ^{13}C NMR analysis allowed us to correlate the chemical shifts of pyridazine ring atoms with substituents at N-2 and C-6. The obtained results showed that the 5 position is affected most by structural changes both in N-2 and in C-6.

Experimental

Mass spectra were recorded on VG Autoespec M, MICROTOF FOCUS, and Bruker FTMS APEX XIII spectrometers. NMR spectra were recorded on a Bruker ARX400 spectrometer (400.13 MHz for ^{1}H NMR and 100.62 MHz for ^{13}C NMR) from samples as approximately 50 mM solutions in $CDCl_3$ or CD_3OD at 300 K in 5 mm outside diameter tubes. The chemical shifts were internally referenced to $CDCl_3$ signals (δ = 7.26 ppm for ^{1}H; δ = 77.0 ppm for ^{13}C) or CD_3OD signals (δ = 4.84 ppm for ^{1}H; δ = 49.05 ppm for ^{13}C). The pulse conditions were as follows: for the ^{1}H NMR spectrum, 30° pulse flip angle, acquisition time (AQ) = 7.18 s, relaxation delay (RD) = 1.0 s, spectral width (SW) = 4562.04 Hz, data points (TD) = 65 536; for the ^{13}C NMR spectrum, 30° pulse flip angle, AQ = 1.42 s, RD = 2.0 s, SW = 23 148.15 Hz, TD = 65 536; for the DEPT-135 spectrum, AQ = 1.42 s, RD = 1.0 s, SW = 23 148.15 Hz, TD = 65 536; for the NOE-difference spectrum, AQ = 3.98 s, RD = 2.0 s, SW = 8223.69 Hz, TD = 65 536; for the COSY spectrum, AQ = 0.14 s, RD = 1.49 s, SW = 3597.12 Hz, TD = 1024; for the gHSQC spectrum, AQ = 0.17 s, RD = 1.5 s, SW = 3041.36 Hz, TD = 1024; for the HMBC spectrum, AQ = 0.17 s, RD = 1.5 s, SW = 3041.36 Hz, TD = 1024. Data processing was carried out with Bruker UXNMR programs.

The 2-alkylfurans **1a**–**c** were prepared as described elsewhere.[14]

5-(*tert*-Butyldiphenylsilyloxymethyl)-5-methoxy-5*H*-furan-2-one (2a)

Compound **2a** (1.95 g, 56%) was obtained from **1a** (3.06 g, 9.10 mmol) following a previously reported procedure.[14a] ^{1}H NMR ($CDCl_3$, δ): 7.62 (m, 4H, H-Ph), 7.40 (m, 6H, H-Ph), 7.09 (d, 1H, J = 5.7 Hz, H3), 6.29 (d, 1H, J = 5.7 Hz, H4), 3.88 (s, 2H, CH_2), 3.24 (s, 3H, CH_3O), 1.01 (s, 9H, 3xCH_3). ^{13}C NMR ($CDCl_3$, δ): 169.8 (C2), 152.1 (C4), 135.6 (CH-Ph), 132.4 (C-Ph), 129.9 (CH-Ph), 127.8 (CH-Ph), 126.1 (C3), 110.3 (C5), 65.2 (CH_2), 51.4 (CH_3O), 26.7 [$(CH_3)_3$], 19.2 [$C(CH_3)_3$].

General procedure for the preparation of 4-hydroxybutenolides 2b and 2c

A solution of **1b**–**c** (1.7-8.3 mmol), *N*,*N*-diisopropylethylamine (4.5 equiv.), 4,5,6,7-tetrachloro-2′,4′,5′,7′-tetraiodofluorescein disodium salt (rose Bengal; 15 mg) in MeOH (15–35 ml), previously purged with O_2, was irradiated with a 200-W lamp for 4 h at −78 °C, stirring under oxygen atmosphere. After the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (30 ml), and 0.12 M oxalic acid in H_2O (4 equiv.) was added. The mixture was stirred for 30 min at room temperature (RT) and extracted with CH_2Cl_2 (3 × 30 ml). After removal of the solvent, the residue obtained was rapidly passed through a column chromatography on silica gel (hexane–EtOAc, 2:1) to afford the corresponding 4-hydroxybutenolide as a crude oil.

5-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-5-hydroxy-5*H*-furan-2-one (2b)

In total, 569 mg was obtained from **1b** (610 mg, 1.74 mmol). ^{1}H NMR ($CDCl_3$, δ): 7.73 (m, 4H, H-Ph), 7.46 (m, 6H, H-Ph), 7.29 (d, 1H, J = 5.6 Hz, H3), 6.09 (d, 1H, J = 5.6 Hz, H4), 4.31 (m, 1H, 1H2′), 3.89 (m, 1H, 1H2′), 2.34 (m, 1H, 1H1′), 1.90 (m, 1H, 1H1′), 1.11 (s, 9H, 3 × CH_3).

5-[3-(*tert*-Butyldiphenylsilyloxy)propyl]-5-hydroxy-5*H*-furan-2-one (2c)

In total, 3.80 g was obtained from **1c** (3.02 g, 8.28 mmol). Spectroscopic data for **2c** is in accordance with the literature.[15]

General procedure for the preparation of pyridazinones 3 and 4

To a solution of compound **2a**–**c** (0.7–2.2 mmol) in ethanol (6–10 ml), a solution of hydrazine monohydrate or methylhydrazine (2.5 equiv.) in ethanol (1.5 ml) was added. The reaction mixture was stirred under reflux for 3 h (**2a**) or at 0 °C for 15 min (**2b**–**c**). After removal of the solvent, the residue was purified by column chromatography on silica gel to afford the corresponding pyridazinone.

6-(*tert*-Butyldiphenylsilyloxymethyl)pyridazin-3(2*H*)-one (3a)

Yield: 14%; High resolution mass spectrometry-electrospray ionization (HRMS-ESI): *m/z* calcd. for $C_{21}H_{25}N_2O_2Si$, 365.16798 [M + H]; found 365.16704.

6-(*tert*-Butyldiphenylsilyloxymethyl)-2-methylpyridazin-3(2*H*)-one (4a)

Yield: 41%; HRMS-ESI: *m/z* calcd. for $C_{22}H_{27}N_2O_2Si$, 379.18363 [M + H]; found 379.18331.

6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]pyridazin-3(2*H*)-one (3b)

Yield: 34% (two steps); HRMS-ESI: *m/z* calcd. for $C_{22}H_{27}N_2O_2Si$, 379.18363 [M + H]; found 379.18344.

6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-2-methylpyridazin-3(2*H*)-one (4b)

Yield: 11% (two steps); HRMS-ESI: *m/z* calcd. for $C_{23}H_{29}N_2O_2Si$, 393.19928 [M + H]; found 393.19894.

6-[3-(*tert*-Butyldiphenylsilyloxy)propyl]pyridazin-3(2*H*)-one (3c)

Yield: 45% (two steps); HRMS-ESI: *m/z* calcd. for $C_{23}H_{29}N_2O_2Si$, 393.19928 [M + H]; found 393.19804.

6-[3-(*tert*-Butyldiphenylsilyloxy)propyl]-2-methylpyridazin-3(2*H*)-one (4c)

Yield: 31% (two steps); HRMS-ESI: *m/z* calcd. for $C_{24}H_{31}N_2O_2Si$, 407.21493 [M + H]; found 407.21514.

General procedure for the preparation of 2-benzylpyridazinones 5

A solution of the appropriate pyridazinone (0.05 mmol) in tetrahydrofuran (THF) (2 ml) was added, dropwise at 0 °C, to a suspension of NaH (1.5 equiv., 60% dispersion in mineral oil) in THF (2 ml). After the mixture was stirred at RT for 1 h, BnBr (3 equiv.) and Bu_4NI (0.2 equiv.) were added. The reaction mixture was stirred at RT for 2 h, followed by quenching with MeOH. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane–EtOAc, 3 : 1) to afford the corresponding 2-benzylpyridazinone.

2-Benzyl-6-(*tert*-butyldiphenylsilyloxymethyl)pyridazin-3(2*H*)-one (5a)

Yield: 68%; HRMS-ESI: *m/z* calcd. for $C_{28}H_{31}N_2O_2Si$, 455.21493 [M + H]; found 455.21443.

2-Benzyl-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]pyridazin-3(2*H*)-one (5b)

Yield: 70%; HRMS-ESI: *m/z* calcd. for $C_{29}H_{33}N_2O_2Si$, 469.23058 [M + H]; found 469.23109.

2-Benzyl-6-[3-(*tert*-butyldiphenylsilyloxy)propyl]pyridazin-3(2*H*)-one (5c)

Yield: 61%; HRMS-ESI: *m/z* calcd. for $C_{30}H_{35}N_2O_2Si$, 483.24623 [M + H]; found 483.24544.

General procedure for the preparation of 6-hydroxyalkylpyridazinones 6–8

A solution of the appropriate pyridazinone (0.07–0.38 mmol), 1 M tetrabutylammonium fluoride (TBAF) in THF (1.1 equiv.) in THF (3–8 ml) was stirred at RT for 15 min. After quenching with a few drops of sat. aq. $NaHCO_3$, and drying with Na_2SO_4, the solvent was evaporated. The residue was purified by column chromatography on silica gel (EtOAc–MeOH, 95 : 5) to afford the corresponding 6-hydroxyalkylpyridazinone.

6-Hydroxymethylpyridazin-3(2*H*)-one (6a)

Yield: 86%; High resolution mass spectrometry-electronic impact (HRMS-EI): *m/z* calcd. for $C_5H_6N_2O_2$, 126.0429; found 126.0430.

6-(2-Hydroxyethyl)pyridazin-3(2*H*)-one (6b)

Yield: 94%; HRMS-EI: *m/z* calcd. for $C_6H_8N_2O_2$, 140.0586; found 140.0589.

6-(3-Hydroxypropyl)pyridazin-3(2*H*)-one (6c)

Yield: 99%; HRMS-ESI: *m/z* calcd. for $C_7H_{11}N_2O_2$, 155.08150 [M + H]; found 155.08176.

6-Hydroxymethyl-2-methylpyridazin-3(2*H*)-one (7a)

Yield: 99%; HRMS-EI: *m/z* calcd. for $C_6H_8N_2O_2$, 140.0586; found 140.0580.

6-(2-Hydroxyethyl)-2-methylpyridazin-3(2*H*)-one (7b)

Yield: 99%; HRMS-EI: *m/z* calcd. for $C_7H_{10}N_2O_2$, 154.0742; found 154.0749.

6-(3-Hydroxypropyl)-2-methylpyridazin-3(2*H*)-one (7c)

Yield: 98%; HRMS-EI: *m/z* calcd. for $C_8H_{12}N_2O_2$, 168.0899; found 168.0905.

2-Benzyl-6-hydroxymethylpyridazin-3(2*H*)-one (8a)

Yield: 98%; HRMS-EI: *m/z* calcd. for $C_{12}H_{12}N_2O_2$, 216.0899; found 216.0900.

2-Benzyl-6-(2-hydroxyethyl)pyridazin-3(2*H*)-one (8b)

Yield: 97%; HRMS-ESI: *m/z* calcd. for $C_{13}H_{14}N_2NaO_2$, 253.0948 [M + Na]; found 253.0937.

2-Benzyl-6-(3-hydroxypropyl)pyridazin-3(2*H*)-one (8c)

Yield: 98%; HRMS-ESI: *m/z* calcd. for $C_{14}H_{17}N_2O_2$, 245.12845 [M + H]; found 245.12816.

Acknowledgements

We acknowledge the Universidade de Vigo and Xunta de Galicia (PGIDIT07PXIB, INCITE08ENA314019ES, INCITE09E1R314094ES and IN845B-2010/020) for financial support. P. B. thanks the Xunta de Galicia for an Isidro Parga Pondal contract.

References

[1] (a) S.-G. Lee, J.-J. Kim, H.-K. Kim, D.-H. Kweon, Y.-J. Kang, S.-D. Cho, S.-K. Kim, Y.-J. Yoon, *Curr. Org. Chem.* **2004**, *8*, 1463; (b) J. J. Bourguignon, S. Oumouch, M. Schmitt, *Curr. Org. Chem.* **2006**, *10*, 277.

[2] P. Mátyus, B. U. W Maes, Z. Riedl, G. Hajós, G. L. F Lemiere, P. Tapolcsányi, K. Monsieurs, O. Éliás, R. A. Dommisse, G. Krajsovszky, *Synlett* **2004**, 1123.

[3] (a) H. Frank, G. Heinisch, in *Progress in Medicinal Chemistry*, vol. 29 (Eds: G. P. Ellis, D. K. Luscombe), Elsevier: Amsterdam, **1992**, pp. 141; (b) V. Dal Piaz, S. Pieretti, C. Vergelli, M. C. Castellana, M. P. Giovannoni, *J. Heterocyl. Chem.* **2002**, *39*, 523.

[4] (a) J. A. Bristol, I. Sircar, W. H. Moos, D. B. Evans, R. E. Weishaar, *J. Med. Chem.* **1984**, *27*, 1099; (b) A. A. Siddiqui, R. Mishra, M. Shaharyar, *Eur. J. Med. Chem.* **2010**, *45*, 2283; (c) E. Sotelo, N. Fraiz, M. Yáñez, V. Terrades, R. Laguna, E. Cano, E. Raviña, *Bioorg. Med. Chem.* **2002**, *10*, 2873.

[5] W. H. Moos, C. C. Humblet, I. Sircar, C. Rithner, R. E. Weishaar, J. A. Bristol, A. T. McPhail, *J. Med. Chem.* **1987**, *30*, 1963.

[6] L. Betti, F. Corelli, M. Floridi, G. Giannaccini, L. Maccari, F. Manetti, G. Strappaghetti, M. Botta, *J. Med. Chem.* **2003**, *46*, 3555.

[7] A. Coelho, E. Raviña, N. Fraiz, M. Yáñez, R. Laguna, E. Cano, E. Sotelo, *J. Med. Chem.* **2007**, *50*, 6476.

[8] K. Abouzid, S. A. Bekhit, *Bioorg. Med. Chem.* **2008**, *16*, 5547.

[9] Z. K. Sweeney, J. P. Dunn, Y. Li, G. Heilek, P. Dunten, T. Elworthy, X. Han, S. H. Harris, D. R. Hirschefeld, J. H. Hogg, W. Huber, A. C. Kaiser, D. J. Kertesz, W. Kim, T. Mirzadegan, M. G. Roepel, Y. D. Saito, T. M. P. C. Silva, S. Swallow, J. L. Tracy, A. Villasenor, H. Vora, A. S. Zhou, K. Klumpp, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4352.

[10] (a) G. Heinisch, W. Holzer, *Can. J. Chem.* **1991**, *69*, 972; (b) A. R. Katritzky, B. E.-D. M. El-Gendy, B. Draghici, D. Fedoseyenko, A. Fadli, E. Metais, *Magn. Reson. Chem.* **2010**, *48*, 397; (c) V. Dal Piaz, A. Graziano, N. Haider, W. Holzer, *Magn. Reson. Chem.* **2005**, *43*, 240; (d) W. Holzer, G. A. Eller, S. Schöenberger, *Heterocycles* **2008**, *75*, 77; (e) N. Haider, W. Holzer, in *Science of Synthesis*, vol. 16 (Ed: Y. Yamamoto), Thieme: Stuttgart, **2004**, pp. 125.

[11] T. Costas, P. Besada, A. Piras, L. Acevedo, M. Yañez, F. Orallo, R. Laguna, C. Terán, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6624.

[12] (a) G. B. Barlin, M. D. Fenn, *Aust. J. Chem.* **1979**, *32*, 2297; (b) W. Holzer, G. A. Eller, S. Schöenberger, *Heterocycles* **2008**, *75*, 77.

[13] H. McNab, *J. Chem. Soc. Perkin Trans.* **1983**, *1*, 1203.

[14] (a) D. Alonso, M. Pérez, G. Gómez, B. Covelo, Y. Fall, *Tetrahedron* **2005**, *61*, 2021; (b) M. Pérez, P. Canoa, G. Gómez, C. Terán, Y. Fall, *Tetrahedron Lett.* **2004**, *45*, 5207; (c) K. C. Nicolaou, R. J. Aversa, J. Jin, F. Rivas, *J. Am. Chem. Soc.* **2010**, *132*, 6855.

[15] A. Fall, M. Sène, E. Tojo, G. Gómez, Y. Fall, *Synthesis* **2010**, 3415.