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Tetrahedron 60 (2004) 12177–12189

Pyridazine derivatives. Part 39: Reactivity of 5-iodopyridazin-3(2*H*)-ones in palladium-catalysed reactions☆

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Received 11 June 2004; revised 4 October 2004; accepted 7 October 2004

Available online 27 October 2004

Abstract—In the search for novel antiplatelet agents, convenient and efficient methods for the preparation of 2,5-disubstituted pyridazin-3(2*H*)-ones are reported that utilise palladium-catalysed cross-coupling reactions. A post-coupling base-promoted isomerisation has been observed during Sonogashira alkynylation of 5-iodopyridazin-3(2*H*)-ones (**3**) with 1-phenyl-2-propyn-1-ol. Variable amounts of phthalazinones were isolated as by-products during the Heck alkenylation of **3**. The usefulness of the hydroxymethyl fragment as a protecting group during the synthesis of 5-substituted pyridazin-3(2*H*)-ones has been validated.
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1. Introduction

In recent years, almost every part of the drug discovery processes has undergone a radical change. However, one of the few things that has not changed is the fact that the majority of medicines are still small organic molecules and a high proportion of these contain a heterocyclic ring.[2] As a consequence, low molecular weight heterocycles have a central role in the development of therapeutic agents. In this area the issues of bioavailability and toxicity must be addressed in addition to bioactivity. It is therefore of general interest to medicinal chemists to have straightforward synthetic methodologies that provide access to a large number of bioactive molecules. For these reasons, atom-efficient transformations and reactions that have high exploratory power are especially desirable during the processes of lead finding and lead optimisation.

In recent decades, the use of transition metal complexes in organic chemistry has fuelled a revolution in this field.[3] Such reactions have allowed the development of new transformations that were either difficult or impossible using previously available methods. Curiously, however, references describing the systematic use of these transformations as part of pharmacomodulation processes for bioactive prototypes have, to the best of our knowledge, not appeared. Palladium chemistry involving heterocycles has unique characteristics stemming from the inherently different structural and electronic properties of heterocycles in comparison to the corresponding carbocyclic aryl compounds.[4] The α and γ activation of heteroaryl halides means that Pd-catalysed chemistry may occur regioselectively at the activated positions, a phenomenon rarely seen in carbocyclic aryl halides.[5–7] Curiously, despite the useful nature of pyridazines, until a few years ago only a limited number of synthetic approaches to achieve substitution on these electron-deficient rings had been described.[8] A number of methods have recently been reported in the literature and, of these, reactions involving organometallics have proved to be powerful tools for the preparation of the desired compounds.[9]

In the last two decades, our research group has explored the chemistry[10] and pharmacology[11] of pyridazine derivatives. Initially, the well known properties of 3-hydrazinopyridazines as direct vasodilators attracted our attention[12] but, more recently, discovering of novel pyridazinone-based antiplatelet agents has become our goal.[13–16] These studies have recently involved the use of different

☆ For the previous paper in this series, see Ref. 1.

Keywords: Pyridazinones; Palladium; Platelets; Ene-adducts; Crystal structure.
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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.014

palladium-catalysed reactions,[17–20] which have demonstrated their versatility as tools to perform the pharmacomodulation and structural diversification at the 5-position of the 6-phenylpyridazin-3(2*H*)-one system.[16] We recently described the antiplatelet activity of compounds **I**[13] (Fig. 1) and the discovery of several 5-alkylidene-6-phenylpyridazin-3(2*H*)-ones **II**[14] and **III**[16] (Fig. 1), which are potent antiplatelet agents. Another interesting result concerning the biological activity of these derivatives is related to their mechanism of action, which is different to other antiplatelet agents that are already available. Recent experiments on these compounds suggested that their antiplatelet effect is related to their ability to affect protein phosphorylation.[13,14]

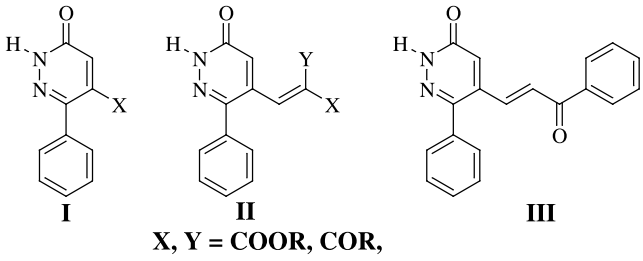


Figure 1.

Preliminary results from the structure–activity relationship (SAR) studies performed on this family of compounds have suggested that the presence of the phenyl group at position 6 and the presence of a free NH at position 2 of the heterocyclic ring (Fig. 1) may not be essential structural requirements for biological action in this new mechanism of action.[21] In order to validate this hypothesis, we became interested in the synthesis of 5-functionalised pyridazin-3(2*H*)-ones **IV**, which have different substituents at position 5 and the appropriate group at position 2 (Me, Bn, H) but do not incorporate the phenyl group at position 6 (Fig. 2). The approach selected to obtain 2,5-disubstituted pyridazin-3(2*H*)-ones **IV** involved the use of palladium-catalysed cross-coupling reactions[22] following the well known Suzuki,[23] Heck,[24] Stille[25] or Sonogashira[26] methodologies. These methods allowed the rapid and efficient introduction of a wide range of substituents at position 5 of the heterocycle.

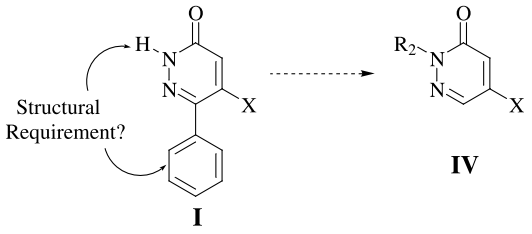


Figure 2.

2. Results and discussion

In order to achieve this objective, different 2-substituted 5-iodopyridazin-3(2*H*)-ones **3** were chosen as starting materials (Scheme 1). Some of these derivatives have been previously described by Mátyus[27a,b] (**3a** and **3b**) but, to the best of our knowledge, only very recently a detailed synthetic procedure to obtain **3a** been published.[27c] These derivatives were obtained by halogen exchange reactions followed by reductive dehalogenation.[27]

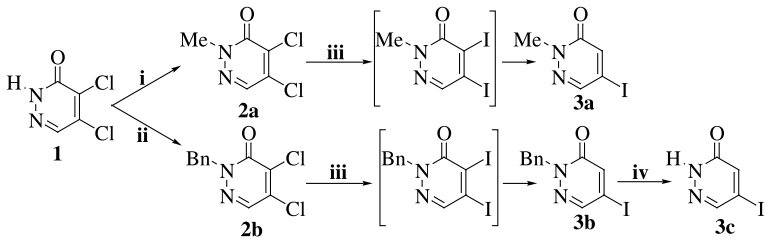
Commercially available 4,5-dichloropyridazin-3(2*H*)-one (**1**) was conveniently N-alkylated by treatment with methyl iodide or benzyl bromide to afford 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones **2** (Scheme 1).[28] Treatment of **2** with a large excess of 57% hydriodic acid under reflux during 24 h yielded the corresponding 2-substituted 5-iodopyridazin-3(2*H*)-ones **3** (Scheme 1). It is worth mentioning here that, as reported by Mátyus,[27] the main intermediates during these transformations are the corresponding 2-substituted 4,5-diiodopyridazin-3(2*H*)-ones, which can be isolated in high yields if reaction times are shorter (3 h) or on using dioxane as the solvent (see Section 3). 5-Iodopyridazin-3(2*H*)-one **3c** was obtained by removing the benzyl group in **3b** by treatment with anhydrous aluminium chloride in dry toluene.[29]

Once a small subset of 5-iodopyridazin-3(2*H*)-ones had been obtained, we proceeded to study the functionalisation of the 5 position of the heterocyclic scaffolds **3** (Scheme 2) using Suzuki, Heck, Stille or Sonogashira cross-coupling reactions. First, the palladium-catalysed transformations were studied for the 2-benzyl- and 5-iodo-2-methylpyridazin-3(2*H*)-ones **3a** and **3b**, which have a non-tautomeric carbonyl group (Schemes 2–5).

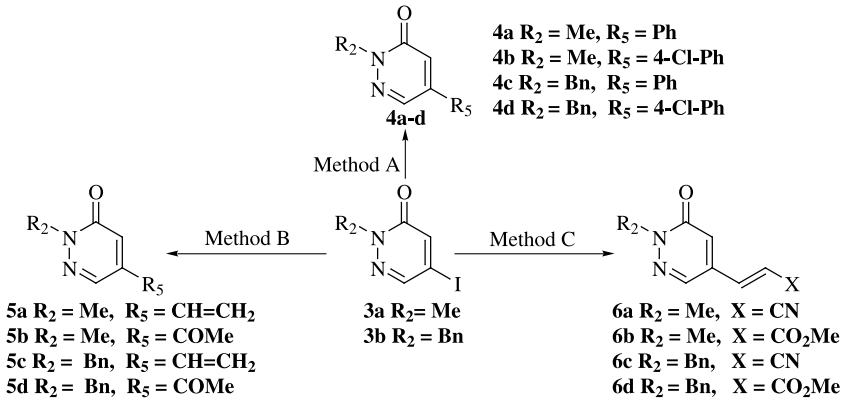
Arylation of compounds **3a** and **3b** was smoothly performed by reaction with the 4-chlorophenyl- or phenylboronic acids in the presence of sodium carbonate as a base and tetrakis(triphenylphosphine)palladium as a palladium source in a 3:1 mixture of dimethoxyethane/water (Scheme 2). This process afforded the corresponding 2-substituted 5-arylpyridazin-3(2*H*)-ones **4a–f** in excellent yields (Table 1). While our work was in progress, a paper was published by Mátyus et al. concerning the synthesis of compound **4a** and other 5-(aryl)-2-methylpyridazin-3(2*H*)-ones as part of the synthesis of new pyridazino[4,5-*b*]indoles.[30]

Pyridazinones **5** were obtained in excellent yields (Table 1) by Stille cross-coupling of **3a–b** with tributyl vinyl stannane or tributylethoxyvinyl stannane at room temperature (Scheme 2). The 5-acetyl-derivatives **5b** and **5d** were prepared in a one-pot procedure by cleavage of the corresponding enol-ether intermediate with 3 N hydrochloric acid.

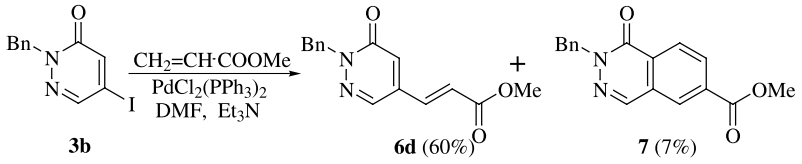
The introduction of alkenyl groups at position 5 in **3a–b** was achieved by coupling with methyl acrylate or acrylonitrile in dimethylformamide under the basic conditions provided by triethylamine (Scheme 2). Different palladium sources were tested for the Heck alkenylation of the heterocycle. Firstly, methods were studied that employ cocktails of palladium catalysts/phosphines [$Pd(OAc)_2$/PPh_3, $PdCl_2(PPh_3)_2$, $PdCl_2[P(o\text{-Tolyl})_3]_2$] and, secondly, the use of palladium on charcoal under phosphine-free conditions was investigated.[24] In all experiments, the expected 5-alkenylpyridazin-3(2*H*)-ones **6** were obtained but it was found that $PdCl_2[P(o\text{-Tolyl})_3]_2$ was a superior



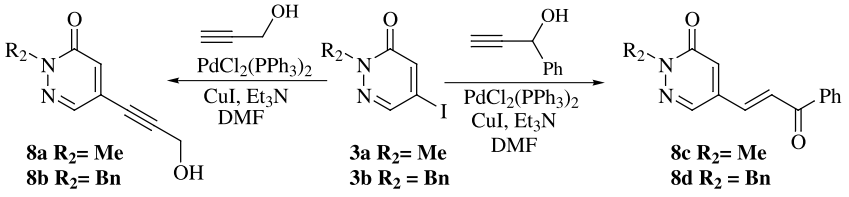
Scheme 1. (i) Me-I/K_2CO_3/Bu_4NBr/acetonitrile, (ii) Bn-Br/K_2CO_3/Bu_4NBr/acetonitrile, (iii) 57% HI, (iv) $AlCl_3$/toluene.



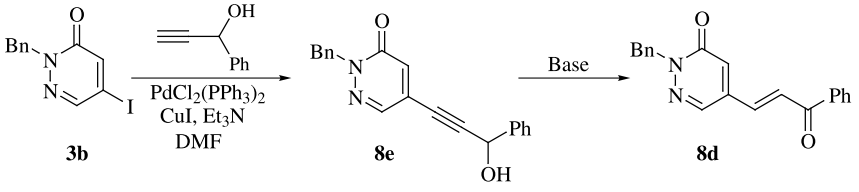
Scheme 2. Method A: $ArB(OH)_2$/$Pd(PPh_3)_4$/Na_2CO_3/DME–H_2O. Method B: R-$Sn(Bu)_3$/$PdCl_2(PPh_3)_2$/Et_3N/DMF/for compounds **5b** and **5d** then 3 N HCl. Method C: CH_2═CH–X/ $PdCl_2[P(o\text{-Tolyl})_3]_2$/$Et_3N$/DMF.



Scheme 3.

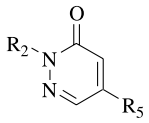


Scheme 4.



Scheme 5.

Table 1. Structure of the obtained 2,5-substituted pyridazin-3(2*H*)-ones



Compound	R_2	R_5	Yield (%)	Compound	R_2	R_5	Yield (%)
4a	Me	Ph	91	**6d**	Bn	CH=CH–CO_2Me	68
4b	Me	4-Cl–Ph	90	**8a**	Me	≡–CH_2-OH	70
4c	Bn	Ph	94	**8b**	Bn	≡–CH_2-OH	93
4d	Bn	4-Cl–Ph	90	**8c**	Me	CH=CH–CO-Ph	89
5a	Me	CH=CH_2	90	**8d**	Bn	CH=CH–CO–Ph	70
5b	Me	CO–Me	70	**8e**	Bn	≡–CH(OH)–Ph	30
5c	Bn	CH=CH_2	78	**10a**	H	CH=CH_2	65
5d	Bn	CO–Me	68	**10b**	H	Ph	60
6a	Me	CH=CH–CN	60	**10c**	H	≡–CH_2-OH	88
6b	Me	CH=CH–CO_2Me	63	**10d**	H	CH=CH–CO-Ph	60
6c	Bn	CH=CH–CN	60	**10e**	H	CH=CH–CO_2Me	62

catalyst for these processes and gave the corresponding functionalised alkenes **6** in yields in the range 40–70%. In contrast to similar experiments on the 5-bromopyridazin-3(2*H*)-ones,[1] we did not find any evidence of dehalogenation during Heck alkenylation of **3a–b**, most probably due to the superior reactivity of the iodo-substituent.

Although the procedures described above give the 5-alkenylpyridazin-3(2*H*)-ones **6a–d** as the main products, an exhaustive investigation of the transformation allowed the isolation of small amounts (5–15%) of phthalazinones as by-products. For instance, the Heck alkenylation of **3b** with methyl acrylate gave, in addition to the expected acrylate **6d** (60%), the phthalazinone **7** (7%) (Scheme 3).

The structure of the unexpected phthalazinones was unambiguously established by analytical and spectroscopic methods (see Section 3). The presence of the methoxycarbonyl group at position 6 of phthalazinone **7** suggests that a highly regioselective process is operating during its formation.

Preliminary mechanistic proposals to explain the formation of phthalazinones during this reaction have recently been put forward.[1] It is thought that this process involves a tandem reaction that initially follows a Heck sp^2 cascade due to a second insertion of another olefin molecule into the previously formed σ-alkylpalladium complex. Further experiments are now in progress to study the mechanism of such a transformation in greater detail and to evaluate the scope of this reaction in the synthesis of 2,6-disubstituted-1-phthalazinones.

Standard Sonogashira conditions[26] were employed to perform the alkynylation at position 5 of the heterocycle (Scheme 4). Although these optimised conditions proved to be applicable to 2-propyn-1-ol (Scheme 4, compounds **8a–b**), the cross-coupling of **3a–b** with 1-phenyl-2-propyn-1-ol (Scheme 4) did not give the expected 2-substituted 5-(3-hydroxy-3-phenylprop-1-yn-yl)pyridazin-3(2*H*)-ones. Instead, the isomeric *E*-chalcones **8c–d** were obtained in good yields (Table 1).

The structure of the heterocyclic chalcones **8c–d** was established on the basis of the analytical and spectroscopic data (see Section 3). The ^{1}H NMR spectra of these products contain doublets with a coupling constant of 15–16 Hz, which confirms a *trans* stereochemistry for the double bond. It is worth noting that this reaction produces the chalcones **8c–d** with an *E*-selectivity greater than 95% after isolation and purification by column chromatography. Other NMR experiments and, in particular, the data extracted form X-ray crystallography on a monocrystal of compound **8c** confirmed our assignment (Fig. 3).

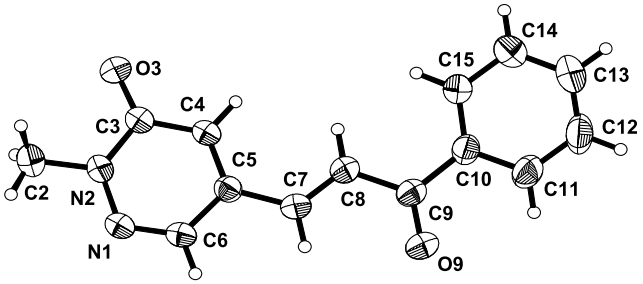


Figure 3. Plot showing the crystal structure and atomic numbering scheme for **8c**. Displacement ellipsoids are drawn at 50% probability level for non-H atoms.

The crystal structure of **8c** is essentially planar and shows a *trans* configuration (Fig. 3). The crystal structure is stabilised by means of weak intermolecular interactions (Fig. 4) of the type C–H···O [C4···O3 = 3.404(3) Å and C6···O9 = 3.332(3) Å]. A weak intramolecular interaction of the type C–H···O is also present [C7···O9 = 2.788(3) Å].

Formation of chalcones **8c–d** under these conditions is dissimilar to results described in previous papers concerning the Sonogashira coupling between 1-phenyl-2-propyn-1-ol and different electron-deficient halides.[31–35] Several authors initially proposed that chalcone formation during these transformations could be related to the participation of organo-palladium intermediates,[31–33] but some recent results[35] (and our own findings[20]) have confirmed that a base-catalysed isomerisation of the expected phenyl-substituted propargyl alcohol is a more likely explanation for this transformation.

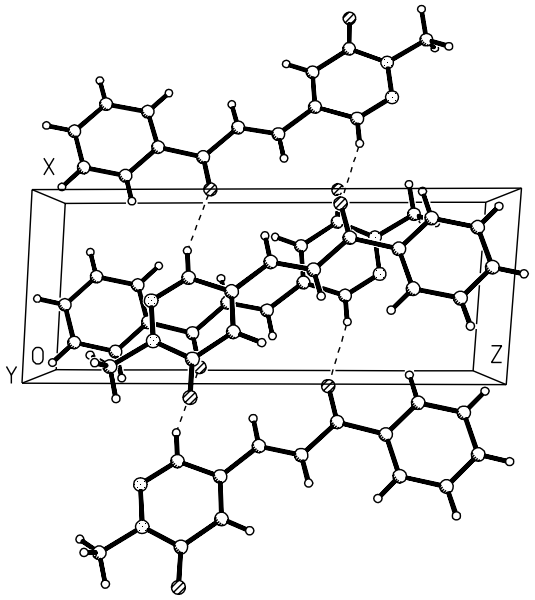


Figure 4. Packing of molecules of **8c** in the unit cell along the [010] crystallographic direction. The most important intermolecular interactions are denoted with dashed lines.

The detailed study of the Sonogashira coupling of **3b** with 1-phenyl-2-propyn-1-ol [by carrying out the reaction at room temperature (25 °C) and after a careful work up] enabled the isolation of the expected phenyl-substituted propargyl alcohol **8e** (30%) together with **8d** (67%) (Scheme 5). Identification of intermediate **8e** is supported by both analytical and spectroscopic data (see Section 3).

Quantitative isolation of **8d** after stirring **8e** in the presence of a base (triethylamine or *N*,*N*-diisopropylethylamine) in a range of solvents (DCM, MeOH, THF, DMF)—even at room temperature—showed that chalcone formation occurs as a consequence of the base-catalysed isomerisation of the phenyl-substituted propargyl alcohol **8e**. This process could be facilitated by the electron-deficient nature of the pyridazinone system, which increases the acidity of the propargylic proton.[36]

The mechanistic pathway proposed for this transformation is outlined in Figure 5. Sonogashira coupling of **3b** with 1-phenyl-2-propyn-1-ol afforded the substituted propargyl alcohol **8e**, which, upon deprotonation at the propargyl centre with triethylamine, led to a propargyl-allenyl anion. Protonation of this species afforded the allene and, finally, the allenol–enone tautomerism furnished the *trans*-configured enone **8d** (Fig. 5).

Our previous work on the 5-bromo-6-phenylpyridazin-3(2*H*)-one showed the low reactivity of this compound in palladium-catalysed reactions.[17–20] However, the high reactivity of the 2-substituted 5-iodopyridazin-3(2*H*)-ones **3a**–**b** (some of the reactions described here can be performed at room temperature) led us to examine such transformations on the 5-iodopyridazin-3(2*H*)-one **3c** on the hypothesis that the change in the halogen (Br→I) could produce an increase in reactivity during the cross-coupling reactions.

Unfortunately, although not completely unexpected, a quick screening experiment with 5-iodopyridazin-3(2*H*)-one **3c** as

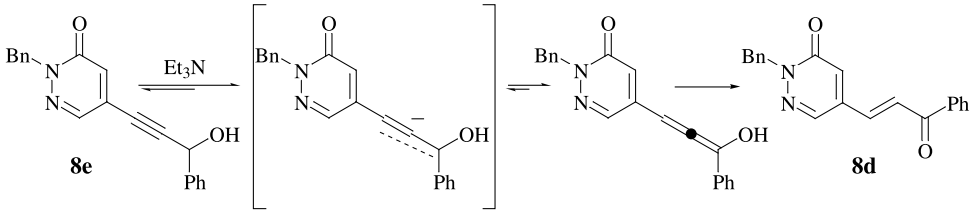
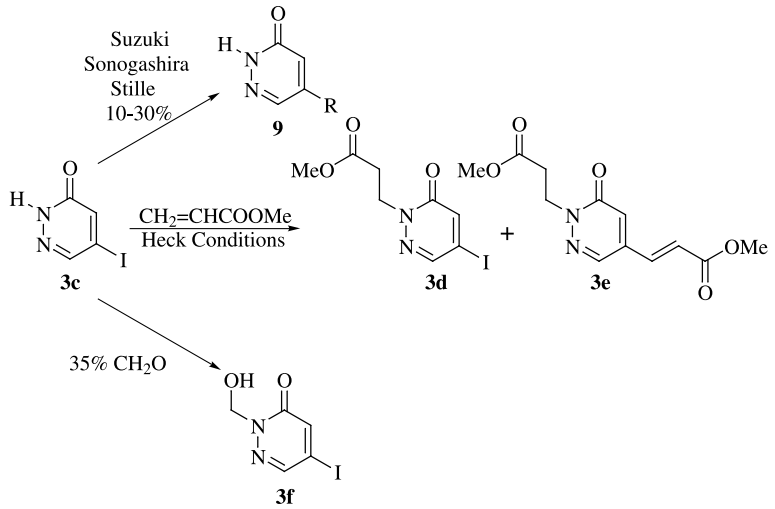


Figure 5.



Scheme 6.

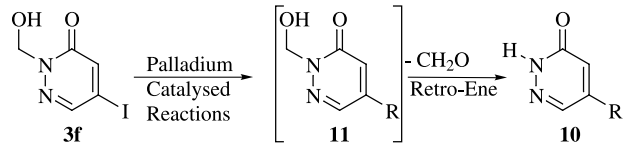
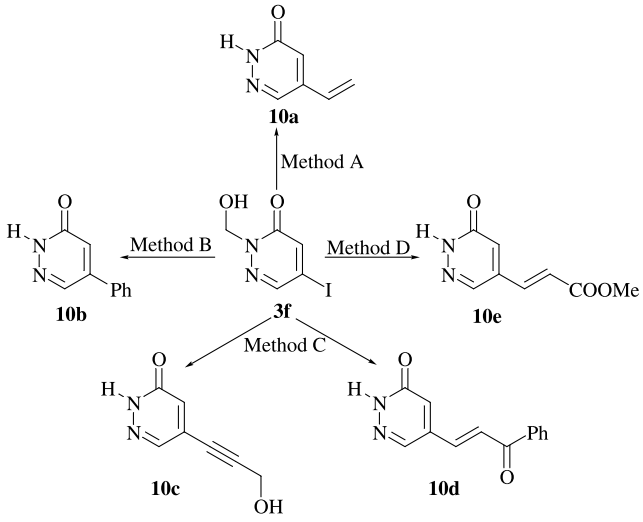


Figure 6.



Scheme 7. Method A: $Bu_3Sn–CH=CH_2/PdCl_2(PPh_3)_2/Et_3N/DMF$. Method B: $PhB(OH)_2$ $Pd(PPh_3)_4/Na_2CO_3/DME–H_2O$. Method C: HC≡C–CH(OH)R/$PdCl_2(PPh_3)_2$/CuI/Et_3N/DMF. Method D: $CH_2=CH–COOMe/PdCl_2[P(o\text{-Tolyl})_3]_2/Et_3N$/DMF.

the starting material under different experimental procedures showed that the degree of transformation was less than 30% during Suzuki, Stille or Sonogashira coupling and most of the starting material was recovered (Scheme 6). All attempts to perform Heck alkenylation of **3c** employing methyl acrylate as the olefin led to formation of *N*-alkyl derivatives **3d** and **3e**. Isolation of these derivatives results from Michael addition of position 2 of the heterocycle to the highly activated and sterically unhindered methyl acrylate. In this transformation, after alkylation at position 2 has been achieved, the Heck alkenylation of **3d** yields the corresponding 5-alkenyl-2-alkylpyridazin-3(2*H*)-one **3e** (Scheme 6).

These results are in accordance with previous studies[17–20] and confirm that a critical factor to ensure the successful coupling is the presence of a group at position 2 of the heterocyclic ring that is able to block the enolisable carbonyl group.

5-Substituted pyridazin-3(2*H*)-ones **9** were prepared using a synthetic strategy recently described by our group that uses a hydroxymethyl group as a thermolabile protecting group for position 2 of the pyridazinone during cross-coupling reactions (Fig. 6).[37]

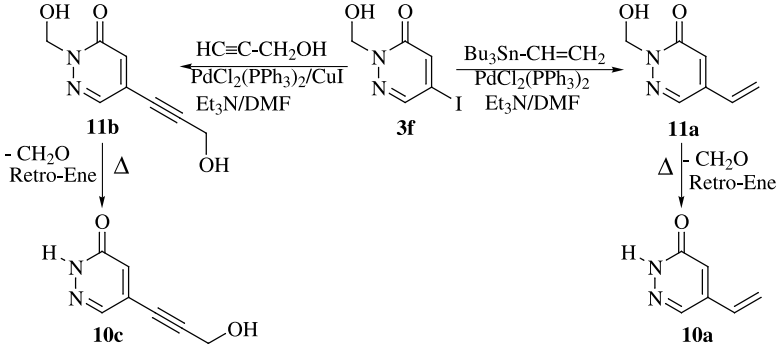
Straightforward hydroxymethylation of **3c** by treatment with 35% formaldehyde solution afforded 2-hydroxymethyl-5-iodopyridazin-3(2*H*)-one **3f** (90%) (Scheme 6). Since pyridazinone **3c** is not reactive under these conditions, the proposed pathway to explain this sequence would involve the initial cross-coupling reactions on **3f** to afford a 5-substituted ene-adduct **9**, which would subsequently lose formaldehyde in a process that may be regarded as a retro-ene fragmentation (Fig. 6).

The excellent reactivity of the 1-O, 3-N, 5-O ene-adduct[38] **3f** toward Suzuki, Sonogashira, Stille or Heck conditions was readily demonstrated by the efficient preparation of different 5-aryl-, 5-alkynyl- or 5-alkenylpyridazin-3(2*H*)-ones **10** in a one-pot procedure (Scheme 7, Table 1).

These results confirm the versatility and usefulness of the hydroxymethyl group as a convenient thermolabile group to protect position 2 of halopyridazinones during palladium-catalysed reactions.

The reactivity of the iodine atom in the ene-adduct **3f** allowed to confirm that formation of compounds **10** is not a concerted process. The isolation and identification of intermediates **11a** and **11b** during some of these transformations, when performed at room temperature, are completely consistent with the pathway shown in Fig. 6 (Scheme 8). Thus, when the starting pyridazinone **3f** was submitted to Stille or Sonogashira cross-coupling reaction conditions at room temperature during 2–3 h, the 5-substituted 2-hydroxymethylpyridazin-3(2*H*)-ones **9** could be isolated from the reaction mixtures. Reactions times greater than 24 h led to 5-substituted pyridazin-3(2*H*)-ones **10**.

Compared to 5-bromo-2-methoxymethyl-6-phenylpyridazin-3(2*H*)-one, the 2-substitued 5-iodopyridazin-3(2*H*)-ones **3** proved to be much more reactive toward



Scheme 8.

palladium-catalysed reactions. This superior reactivity could be due to the change in the halogen, the absence of the phenyl group at position 6 of the heterocycle (which would reduce steric hindrance) or, most probably, a combination of these effects.

In summary, practical and efficient palladium-assisted procedures to perform the structural diversification of the 5-position of 2-substituted pyridazinones have been developed. The palladium-mediated alkynylation of **3** using 1-phenyl-2-propyn-1-ol affords *E*-chalcones in excellent yields. A study of this transformation allowed the isolation of an intermediate and confirmed the electron-deficient nature of the starting 5-iodopyridazin-3(2*H*)-one to be the key factor during the base-catalysed isomerisation process. Furthermore, part of this work has demonstrated the synthetic utility of the 2-hydroxymethyl unit as a convenient protecting group for the lactam function during couplings on 5-iodopyridazin-3(2*H*)-one.

3. Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured using a Perkin–Elmer 1640 FTIR spectrophotometer with samples as potassium bromide pellets. The NMR spectra were recorded on Bruker AM300 and XM500 spectrometers. Chemical shifts are given as δ values against tetramethylsilane as internal standard and J values are given in Hz. Mass spectra were obtained on a Varian MAT-711 instrument. High-resolution mass spectra were obtained on an Autospec Micromass spectrometer. Elemental analyses were performed on a Perkin–Elmer 240B apparatus at the Microanalysis Service of the University of Santiago de Compostela. The reactions were monitored by TLC with 2.5 mm Merck silica gel GF 254 strips, and the purified compounds each showed a single spot; unless stated otherwise, iodine vapour and/or UV light were used for detection of compounds. Commercially available starting materials and reagents were purchased and used without further purification.

The X-ray crystallographic determination of **8c** was performed on a Siemens P4 four-circle diffractometer with graphite monochromated Cu K_α radiation. The intensity data were collected using 2θ–ω scans, with ω scan width equal to the difference of the background and the high ωbackground plus the separation between the $K_{\alpha1}$ and $K_{\alpha2}$ positions; 2792 reflections measured ($3.71<\theta<68.87°$, $-1<h<6$, $-9<k<9$, $-16<l<16$), 2111 unique (merging $R=0.0599$) and 1462 observed [$F^2\geq 2\sigma(F)^2$] reflections. Empirical absorption correction via ψ scans was applied.[39] Three standard reflections were monitored every 100 reflections (intensity decay: 3%).

The crystal structure of **8c** was solved by direct methods and Fourier synthesis. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times *Ueq* of their parent atoms. Data collection: XSCANS.[40] Cell refinement: XSCANS.[40] Data reduction: XSCANS.[40] Program used to solve structure: SIR92.[41] Program used to refine structure: SHELXL97.[42] Molecular graphics: DIAMOND.[43] Software used to prepare material for publication: PLATON.[44]

2-Substituted 4,5-dichloropyridazin-3(2*H*)-ones **2** were obtained by following previously described procedures.[28]

3.1. Synthesis of 2-substituted 5-iodopyridazin-3(2*H*)-ones 3. General procedure

A solution of 2-substituted 4,5-dichloropyridazin-3(2*H*)-one **2** (28 mmol) in 57% hydriodic acid (41 mL) was stirred and heated under reflux (oil bath 140 °C) until the starting material had been consumed (24 h). After cooling, the solution was treated with 30% sodium thiosulphate and then extracted with dichloromethane. The organic phase was dried over sodium sulphate, and concentrated to dryness under reduced pressure. The residue was purified twice by column chromatography on silica gel. Further purification was achieved by recrystallisation from the appropriate solvent.

3.1.1. 5-Iodo-2-methylpyridazin-3(2*H*)-one 3a. Purification by column chromatography on silica gel using AcOEt/hexane (1:3) as eluent. Mp 179–180 °C (isopropanol). Yield 81%. IR (KBr): ν_{max}/cm^{-1} 1654 (CO). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.89 (d, $J=1.9$ Hz, 1H, H_6), 7.44 (d, $J=1.9$ Hz, 1H, H_4), 3.71 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 159.0, 142.0, 138.2, 102.2, 40.3. MS (70 eV) *m/z* (%): 236 (M^+, 100), 208 (42), 165 (82), 127 (55). Anal. Calcd for $C_5H_5IN_2O$, C 25.45, H 2.14, N 11.87; found, C 25.47, H 2.15, N 11.96.

3.1.2. 2-Benzyl-5-iodopyridazin-3(2*H*)-one 3b. Purification by column chromatography on silica gel using AcOEt/hexane (1:8) as eluent. Mp 132–133 °C (isopropanol). Yield 88%. IR (KBr): ν_{max}/cm^{-1} 1654 (CO), 1560 (aromatics). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.91 (d, $J=2.0$ Hz, 1H, H_6), 7.46 (d, $J=2.0$ Hz, 1H, H_4), 7.40 (m, 2H, aromatics), 7.33 (m, 3H, aromatics), 5.25 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 159.0, 142.3, 138.8, 135.9, 129.2, 129.0, 128.5, 102.8, 55.4. MS (70 eV) *m/z* (%): 312 (M^+, 24), 165 (38), 125 (42), 111 (64), 97 (100). Anal. Calcd for $C_{11}H_9IN_2O$, C 42.33, H 2.91, N 8.98; found, C 42.43, H 3.01, N 9.07.

2-Substituted 4,5-diiodopyridazin-3(2*H*)-ones can be successfully obtained employing the general procedure previously described for the 2-substituted 5-iodopyridazin-3(2*H*)-ones **3** but shorting reaction times to 3 h.

3.1.3. 4,5-Diiodo-2-methylpyridazin-3(2*H*)-one. Purification by column chromatography on silica gel using AcOEt/hexane (1:6) as eluent. Mp 156–157 °C (isopropanol). Yield 75%. IR (KBr): ν_{max}/cm^{-1} 1650 (CO). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.80 (s, 1H, H_6), 3.76 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 159.0, 141.4, 121.0, 116.5, 41.8. MS (70 eV) *m/z* (%): 362 (M^+, 88), 333 (28), 270 (100).

3.1.4. 2-Benzyl-4,5-diiodopyridazin-3(2*H*)-one. Purification by column chromatography on silica gel using

AcOEt/hexane (1:8) as eluent. Mp 97–98 °C (isopropanol). Yield 68%. IR (KBr): ν_{max}/cm^{-1} 1651 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.58 (s, 1H, H_6), 7.44 (m, 2H, aromatics), 7.30 (m, 3H, aromatics), 5.32 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 158.6, 145.4, 136.1, 135.5, 135.3, 129.5, 129.1, 128.7, 56.2. MS (70 eV) *m/z* (%): 438 (M^+, 14), 347 (25), 242 (58).

3.1.5. 5-Iodopyridazin-3(2*H*)-one 3c. To a suspension of anhydrous aluminium chloride (0.66 g, 5.03 mmol) in dry toluene (8 mL) under an argon atmosphere was slowly added the 2-benzyl-5-iodopyridazin-3(2*H*)-one **3b** (0.31 g, 1.0 mmol) and the mixture was stirred and heated (oil bath 120 °C) until the starting material had been consumed. After cooling, ice-water was added, the mixture stirred for 10 min and then extracted with dichloromethane. The organic phase was dried over sodium sulphate and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel using AcOEt/hexane (1:10) as eluent. Further purification was achieved by recrystallisation from isopropanol. Mp 147–148 °C (isopropanol). Yield 90%. IR (KBr): ν_{max}/cm^{-1} 3004 (NH), 1651 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 12.57 (bs, 1H, NH), 8.00 (d, $J=1.9$ Hz, 1H, H_6), 7.54 (d, $J=1.9$ Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 161.1, 143.6, 139.1, 105.3. MS (70 eV) *m/z* (%): 222 (M^+, 100), 194 (20), 127 (41). Anal. Calcd for $C_4H_3IN_2O$, C 21.64, H 1.36, N 12.62; found, C 21.64, H 1.45, N 12.66.

3.2. Reaction of methyl acrylate with 3c under Heck conditions (synthesis of 3d and 3e)

A mixture of 5-iodopyridazin-3(2*H*)-one **3c** (1.00 mmol), bis(tri-*o*-tolyl-phosphine)palladium(II) dichloride (0.10 mmol), triethylamine (1.52 mmol) and methyl acrylate (2.00 mmol) in DMF (10 mL) in a sealed tube was heated under reflux (oil bath 110 °C) under argon until the starting material had been consumed. The mixture was allowed to cool to room temperature, filtered through a pad of Celite and the filtrate was evaporated to dryness to give a brown oily residue. The residue was purified by column chromatography (AcOEt/hexane, 1:4) to give **3d** and **3e**. Further purification was achieved by recrystallisation.

3.2.1. Methyl-3-(4-iodo-6-oxo-pyridazin-1(6*H*)-yl)propanoate 3d. Mp 58–60 °C (isopropanol). Yield 9%. IR (KBr): ν_{max}/cm^{-1} 1730 (COO), 1640 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.91 (d, $J=1.9$ Hz, 1H, H_6), 7.46 (d, $J=1.9$ Hz, 1H, H_4), 4.38 (t, $J=7.1$ Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 2.81 (t, $J=7.1$ Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.6, 158.9, 142.3, 138.6, 103.0, 52.3, 47.7, 39.6. MS (70 eV) *m/z* (%): 308 (M^+, 34), 249 (49), 222 (100). HRMS *m/z* calcd for $C_8H_9IN_2O_3$ (M^+): 307.9658, found: 307.9660.

3.2.2. Methyl (2*E*)-3-[1-(3-methoxy-3-oxopropyl)-6-oxo-1,6-dihydropyridazin-4-yl]acrylate 3e. Mp 120–122 °C (isopropanol). Yield 85%. IR (KBr): ν_{max}/cm^{-1} 1733 (COO), 1636 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.89 (d, $J=2.1$ Hz, 1H, H_6), 7.40 (d, $J=16.1$ Hz, 1H, CH), 6.90 (d, $J=2.1$ Hz, 1H, H_4), 6.53 (d, $J=16.1$ Hz, 1H, CH), 4.41 (t, $J=7.0$ Hz, 1H, H_2), 3.82 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 2.83 (t, $J=7.0$ Hz, 1H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.7, 165.9, 160.3, 138.2, 134.3, 128.2, 125.5, 52.7, 52.3, 47.8, 32.8, 31.3. MS (70 eV) *m/z* (%): 266 (M^+, 55), 234 (45), 207 (40), 179 (100). HRMS *m/z* calcd for $C_{12}H_{14}IN_2O_5$ (M^+): 266.0903, found: 266.0907.

3.2.3. 2-Hydroxymethyl-5-iodopyridazin-3(2*H*)-one 3f. A mixture of **3c** (1.5 g, 6.75 mmol) and 35% formaldehyde (50 mL) was flushed with argon for 5 min. The suspension was stirred and heated under reflux (oil bath 110 °C) under argon until the starting material had been consumed. The mixture was cooled and the suspension was concentrated to dryness under reduced pressure. The resulting solid was purified by column chromatography on silica gel (AcOEt/hexane, 1:3). Further purification was achieved by recrystallisation from isopropanol. Mp 140–141 °C (isopropanol). Yield 90%. IR (KBr): ν_{max}/cm^{-1} 3261 (OH), 1651 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 8.13 (d, $J=2.1$ Hz, 1H, H_6), 7.59 (d, $J=2.1$ Hz, 1H, H_4), 6.77 (t, $J=7.6$ Hz, 1H, OH), 5.25 (d, $J=7.6$ Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 158.3, 142.2, 138.3, 105.7, 73.5. MS (70 eV) *m/z* (%): 252 (M^+, 20), 236 (30), 223 (100). HRMS *m/z* calcd for $C_5H_5IN_2O_2$ (M^+): 251.9396, found: 251.9399.

3.3. General procedure for the Suzuki coupling of 3

The 2-substituted 5-iodopyridazin-3(2*H*)-one **3** (1.7 mmol) was mixed with the corresponding arylboronic acid (2.2 mmol), $Pd(PPh_3)_4$ (0.016 mmol) and K_2CO_3 (5.08 mmol) in a 3:1 mixture of DME/H_2O (15 mL) and flushed with argon for 5 min. The mixture was then stirred and heated under reflux (oil bath 100 °C) under argon until the starting material had been consumed. After cooling, the solution was filtered through a pad of Celite and the filtrate was evaporated to dryness to give an oily residue, which was purified by column chromatography on silica gel. Further purification was achieved by recrystallisation from the appropriate solvent.

3.3.1. 2-Methyl-5-phenylpyridazin-3(2*H*)-one 4a. Purification by column chromatography on silica gel using AcOEt/hexane (1:1) as eluent. Mp 119–120 °C (isopropanol). Yield 91%. IR (KBr): ν_{max}/cm^{-1} 1658 (CO), 1590 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 8.00 (d, $J=2.2$ Hz, 1H, H_6), 7.55 (m, 2H, aromatics), 7.46 (m, 3H, aromatics), 7.00 (d, $J=2.2$ Hz, 1H, H_4), 3.83 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.3, 144.2, 136.0, 134.3, 130.6, 129.8, 127.2, 124.7, 40.3. MS (70 eV) *m/z* (%): 186 (M^+, 40), 158 (28), 130 (10), 115 (100). Anal. Calcd for $C_{11}H_{10}N_2O$, C 70.95, H 5.41, N 15.04; found, C 71.05, H 5.43, N 15.04.

3.3.2. 5-(4′-Chlorophenyl)-2-methylpyridazin-3(2*H*)-one 4b. Purification by column chromatography on silica gel using AcOEt/hexane (1:1) as eluent. Mp 167–168 °C (isopropanol). Yield 90%. IR (KBr): ν_{max}/cm^{-1} 1654 (CO), 1589 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.98 (d, $J=2.3$ Hz, 1H, H_6), 7.52–7.48 (m, 4H, aromatics), 7.00 (d, $J=2.3$ Hz, 1H, H_4), 3.81 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 161.0, 143.0, 137.0, 135.5, 132.7, 130.1, 128, 5, 124.7, 40.4. MS (70 eV) *m/z* (%): 220 (M^+, 48), 192 (20), 149 (100). Anal. Calcd for

$C_{11}H_9ClN_2O$, C 59.88, H 4.11, N 12.70; found, C 60.10, H 4.15, N 12.72.

3.3.3. 2-Benzyl-5-phenylpyridazin-3(2*H*)-one 4c. Purification by column chromatography on silica gel using AcOEt/hexane (1:2) as eluent. Mp 126–127 °C (isopropanol). Yield 94%. IR (KBr): ν_{max}/cm^{-1} 1655 (CO), 1590 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 8.00 (d, $J=2.0$ Hz, 1H, H_6), 7.55–7.46 (m, 7H, aromatics), 7.36–7.27 (m, 3H, aromatics), 7.00 (d, $J=2.0$ Hz, 1H, H_4), 5.37 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.8, 143.9, 136.6, 136.3, 134.2, 130.6, 129.7, 129.1, 129.0, 128.3, 127.2, 125.2, 55.2. MS (70 eV) *m/z* (%): 262 (M^+, 35), 220 (10), 158 (20), 115 (100). Anal. Calcd for $C_{17}H_{14}N_2O$, C 77.84, H 5.38, N 10.68; found, C 77.90, H 5.56, N 10.67.

3.3.4. 2-Benzyl-5-(4-chlorophenyl)pyridazin-3(2*H*)-one 4d. Purification by column chromatography on silica gel using AcOEt/hexane (1:2) as eluent. Mp 145–146 °C (isopropanol). Yield 90%. IR (KBr): ν_{max}/cm^{-1} 1656 (CO), 1588 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 8.00 (d, $J=2.2$ Hz, 1H, H_6), 7.51–7.43 (m, 7H, aromatics), 7.32 (m, 2H, aromatics), 7.00 (d, $J=2.2$ Hz, 1H, H_4), 5.36 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.6, 142.8, 136.8, 136.5, 135.9, 132.7, 130.0, 129.2, 129.0, 128.5, 128.4, 125.3, 55.3. MS (70 eV) *m/z* (%): 312 (M^+, 24), 165 (38), 125 (42), 111 (64), 97 (100). Anal. Calcd for $C_{17}H_{13}ClN_2O$, C 68.81, H 4.42, N 9.44; found, C 69.14, H 4.54, N 9.53.

3.4. General procedure for the Stille coupling of 3

A mixture of 2-substituted 5-iodopyridazin-3(2*H*)-one **3** (3.40 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.16 mmol) and the corresponding tributylstannane (3.73 mmol) in anhydrous toluene (20 mL) was heated under reflux under argon until the starting material had been consumed. The mixture was allowed to cool to room temperature, filtered through a pad of Celite and the filtrate was evaporated to dryness to give a yellow oily residue. For the synthesis of compounds **5b** and **5d** the oily residue containing the corresponding enol-ether was heated under reflux in 3 N hydrochloric acid during 12 h. After extraction with dichloromethane, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography and further purification was achieved by recrystallisation from the appropriate solvent.

3.4.1. 2-Methyl-5-vinylpyridazin-3(2*H*)-one 5a. Purification by column chromatography on silica gel using AcOEt/hexane (1:8) as eluent. Mp 101–102 °C (isopropanol). Yield 90%. IR (KBr): ν_{max}/cm^{-1} 1654 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.83 (d, $J=2.0$ Hz, 1H, H_6), 6.72 (d, $J=2.0$ Hz, 1H, H_4), 6.48 (dd, $J=6.7$, 10.9 Hz, 1H, CH), 5.93 (d, $J=16.6$ Hz, 1H, CH), 5.58 (d, $J=10.9$ Hz, 1H, CH), 3.74 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 161.3, 140.6, 134.4, 131.7, 124.8, 122.1, 40.1. MS (70 eV) *m/z* (%): 136 (M^+, 100), 108 (26). Anal. Calcd for $C_7H_8N_2O$, C 61.75, H 5.92, N 20.58; found, C 61.79, H 5.94, N 20.57.

3.4.2. 5-Acetyl-2-methylpyridazin-3(2*H*)-one 5b. Purification by column chromatography on silica gel using AcOEt/hexane (1:2) as eluent. Mp 145–146 °C (isopropanol). Yield 70%. IR (KBr): ν_{max}/cm^{-1} 1654 (CO), 1560 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 8.15 (d, $J=2.2$ Hz, 1H, H_6), 7.30 (d, $J=2.2$ Hz, 1H, H_4), 3.80 (s, 3H, CH_3), 2.54 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 195.9, 160.9, 137.8, 133.7, 129.5, 40.7, 26.9. MS (70 eV) *m/z* (%): 152 (M^+, 100), 124 (14), 109 (70). Anal. Calcd for $C_7H_8N_2O_2$, C 55.26, H 5.30, N 18.41; found, C 55.32, H 5.42, N 18.46.

3.4.3. 2-Benzyl-5-vinylpyridazin-3(2*H*)-one 5c. Purification by column chromatography on silica gel using AcOEt/hexane (1:6) as eluent. Mp 60–62 °C (isopropanol). Yield 78%. IR (KBr): ν_{max}/cm^{-1} 1653 (CO), 1586 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.91 (d, $J=2.0$ Hz, 1H, H_6), 7.39 (m, 2H, aromatics), 7.28 (m, 3H, aromatics), 6.72 (d, $J=2.0$ Hz, 1H, H_4), 6.44 (dd, $J=6.7$, 11.0 Hz, 1H, CH), 5.88 (d, $J=16.6$ Hz, 1H, CH), 5.54 (d, $J=11.0$ Hz, 1H, CH), 5.27 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.9, 140.5, 136.7, 134.8, 131.7, 129.0, 128.9, 128.2, 125.4, 122.3, 55.1. MS (70 eV) *m/z* (%): 212 (M^+, 75), 91 (62), 65 (100). HRMS *m/z* calcd for $C_{13}H_{12}N_2O$ (M^+): 212.0901, found: 212.0903.

3.4.4. 5-Acetyl-2-benzylpyridazin-3(2*H*)-one 5d. Purification by column chromatography on silica gel using AcOEt/hexane (1:4) as eluent. Mp 105–106 °C (isopropanol). Yield 68%. IR (KBr): ν_{max}/cm^{-1} 1661 (CO), 1547 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 8.17 (d, $J=2.1$ Hz, 1H, H_6), 7.44 (d, $J=2.1$ Hz, 1H, H_4), 7.40 (m, 2H, aromatics), 7.30 (m, 3H, aromatics), 5.33 (s, 2H, CH_2), 2.53 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 196.0, 160.2, 137.3, 135.9, 134.0, 130.2, 129.2, 129.0, 128.6, 55.9, 26.9. MS (70 eV) *m/z* (%): 228 (M^+, 100), 186 (20), 124 (20). Anal. Calcd for $C_{13}H_{12}N_2O_2$, C 68.41, H 5.30, N 12.27; found, C 68.63, H 5.34, N 12.28.

3.5. General procedure for the Heck coupling of 3

A degassed (argon) mixture of the 2-substituted 5-iodopyridazin-3(2*H*)-one **3** (1.00 mmol), bis(tri-*o*-tolylphosphine)-palladium(II) dichloride (0.10 mmol), triethylamine (1.52 mmol) and the corresponding alkene (2.00 mmol) in DMF (10 mL) in a sealed tube was heated under reflux (oil bath 110 °C) under argon until the starting material had been consumed. The mixture was allowed to cool to room temperature, filtered through a pad of Celite and the filtrate was evaporated to dryness to give a brown oily residue. The residue was purified by column chromatography and further purification was achieved by recrystallisation from the appropriate solvent.

3.5.1. (2*E*)-3-(1-Methyl-6-oxo-1,6-dihydropyridazin-4-yl)acrylonitrile 6a. Purification by column chromatography on silica gel using AcOEt/hexane (1:2) as eluent. Mp 155–156 °C (isopropanol). Yield 63%. IR (KBr): ν_{max}/cm^{-1} 2230 (CN), 1670 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.87 (d, $J=2.1$ Hz, 1H, H_6), 7.18 (d, $J=16.7$ Hz, 1H, CH), 6.90 (d, $J=2.1$ Hz, 1H, H_4), 6.07 (d, $J=16.7$ Hz, 1H, CH), 3.77 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.3, 144.3, 136.9, 135.4, 132.8, 127.6, 116.4, 40.4.

MS (70 eV) *m/z* (%): 161 (M^+, 20), 133 (16), 90 (43), 58 (100). Anal. Calcd for $C_8H_7N_3O$, C 59.62, H 4.38, N 26.07; found, C 59.67, H 4.42, N 26.12.

3.5.2. Methyl (2*E*)-3-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)acrylate 6b. Purification by column chromatography on silica gel using AcOEt/hexane (1:2) as eluent. Mp 194–196 °C (isopropanol). Yield 60%. IR (KBr): ν_{max}/cm^{-1} 1723 (COO), 1636 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.87 (d, $J=1.9$ Hz, 1H, H_6), 7.40 (d, $J=16.0$ Hz, 1H, CH), 6.91 (d, $J=1.9$ Hz, 1H, H_4), 6.52 (d, $J=16.0$ Hz, 1H, CH), 3.76 (s, 3H, CH_3), 3.74 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 166.0, 160.6, 138.3, 138.0, 134.0, 127.8, 125.3, 52.6, 40.4. MS (70 eV) *m/z* (%): 194 (M^+, 100), 163 (24), 135 (60). Anal. Calcd for $C_9H_{10}N_2O_3$, C 55.67, H 5.19, N 14.43; found, C 55.71, H 5.19, N 14.45.

3.5.3. (2*E*)-3-(1-Benzyl-6-oxo-1,6-dihydropyridazin-4-yl)acrylonitrile 6c. Purification by column chromatography on silica gel using AcOEt/hexane (1:8) as eluent. Mp 123–125 °C (isopropanol). Yield 68%. IR (KBr): ν_{max}/cm^{-1} 1654 (CO), 1560 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.82 (d, $J=2.2$ Hz, 1H, H_6), 7.52–7.38 (m, 5H, aromatics), 7.12 (d, $J=16.7$ Hz, 1H, CH), 6.89 (d, $J=2.2$ Hz, 1H, H_4), 6.03 (d, $J=16.7$ Hz, 1H, CH), 5.29 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 159.9, 144.3, 136.8, 136.3, 136.0, 130.2, 129.2, 129.0, 128.5, 128.0, 115.3, 55.4. MS (70 eV) *m/z* (%): 237 (M^+, 54), 209 (13), 181 (9), 91 (100). Anal. Calcd for $C_{14}H_{11}N_3O$, C 70.87, H 4.67, N 17.71; found, C 70.89, H 4.88, N 17.75.

3.5.4. Methyl (2*E*)-3-(1-benzyl-6-oxo-1,6-dihydropyridazin-4-yl)acrylate 6d. Purification by column chromatography on silica gel using AcOEt/hexane (1:3) as eluent. 112–113 (isopropanol). Yield 60%. IR (KBr): ν_{max}/cm^{-1} 1726 (COO), 1654 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.90 (d, $J=2.2$ Hz, 1H, H_6), 7.44–7.25 (m, 6H, 5H aromatics + CH), 6.92 (d, $J=2.2$ Hz, 1H, H_4), 6.50 (d, $J=16.1$ Hz, 1H, CH), 5.31 (s, 2H, CH_2), 3.82 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 165.3, 160.0, 138.3, 136.3, 134.3, 129.1, 129.0, 128.5, 128.4, 128.3, 125.3, 55.5, 52.7. MS (70 eV) *m/z* (%): 270 (M^+, 31), 211 (14), 91 (100). Anal. Calcd for $C_{15}H_{14}N_2O_3$, C 66.66, H 5.22, N 10.36; found, C 66.68, H 5.24, N 10.49.

3.5.5. Methyl 2-benzyl-1-oxo-1,2-dihydrophthalazin-6-carboxylate 7. Purification by column chromatography on silica gel using AcOEt/hexane (1:3) as eluent. Mp 156–157 °C (isopropanol). Yield 7%. IR (KBr): ν_{max}/cm^{-1} 1725 (COO), 1645 (CO), 1494 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 8.50 (d, $J=8.50$ Hz, 1H, CH), 8.37–8.33 (m, 2H, aromatics), 8.23 (s, 1H, CH), 7.48–7.41 (m, 2H, aromatics), 7.34–7.25 (m, 3H, aromatics), 5.41 (s, 2H, CH_2), 3.99 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 166.2, 159.5, 138.2, 137.0, 134.7, 132.0, 131.3, 130.5, 129.1, 129.0, 128.3, 128.2, 127.8, 55.2, 53.2. MS (70 eV) *m/z* (%): 294 (M^+, 19), 266 (5), 190 (85). Anal. Calcd for $C_{17}H_{14}N_2O_3$, C 69.38, H 4.79, N 9.52; found, C 69.45, H 4.87, N 9.55.

3.6. General procedure for the Sonogashira coupling of 3

To a degassed (argon) suspension of 2-substituted 5-iodopyridazin-3(2*H*)-one **3** (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol) and CuI (0.02 mmol) in DMF (10 mL) was added triethylamine (2.1 mmol) and the corresponding alkyne (1.50 mmol). The mixture was stirred at room temperature under argon until the starting material had been consumed. The mixture was cooled to room temperature, diluted with dichloromethane and filtered through Celite. The filtrate was concentrated in vacuo and the residue purified by column chromatography on silica gel. Further purification was achieved by recrystallisation from the appropriate solvent.

3.6.1. 2-Methyl-5-(3-hydroxyprop-1-yn-1-yl)pyridazin-3(2*H*)-one 8a. Purification by column chromatography on silica gel using AcOEt/hexane (1:3) as eluent. Mp 134–135 °C (isopropanol). Yield 70%. IR (KBr): ν_{max}/cm^{-1} 3342 (OH), 2210 (C≡C), 1650 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.68 (d, $J=1.9$ Hz, 1H, H_6), 6.99 (d, $J=1.9$ Hz, 1H, H_4), 4.50 (bs, 1H, OH), 3.80 (s, 2H, CH_2), 3.75 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.5, 137.7, 130.5, 128.6, 98.0, 79.1, 51.3, 40.6. MS (70 eV) *m/z* (%): 164 (M^+, 100), 136 (35). Anal. Calcd for $C_8H_8N_2O_2$, C 58.53, H 4.91, N 17.06; found, C 58.61, H 4.89, N 16.97.

3.6.2. 2-Benzyl-5-(3-hydroxyprop-1-yn-1-yl)pyridazin-3(2*H*)-one 8b. Purification by column chromatography on silica gel using AcOEt/hexane (1:2) as eluent. Mp 125–126 °C (isopropanol). Yield 93%. IR (KBr): ν_{max}/cm^{-1} 1640 (CO), 1579 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.64 (d, $J=1.8$ Hz, 1H, H_6), 7.40–7.34 (m, 2H, aromatics), 7.33–7.25 (m, 3H, aromatics), 6.97 (d, $J=1.8$ Hz, 1H, H_4), 5.27 (s, 2H, CH_2), 4.42 (t, $J=6.3$ Hz, 1H, OH), 3.94 (d, $J=6.3$ Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.1, 138.1, 136.0, 131.1, 129.2, 129.0, 128.6, 128.4, 98.4, 79.2, 55.7, 51.2. MS (70 eV) *m/z* (%): 240 (M^+, 44), 213 (8), 184 (14), 156 (10), 136 (23), 104 (36), 91 (100). Anal. Calcd for $C_{14}H_{12}N_2O_2$, C 69.99, H 5.03, N 11.66; found, C 70.06, H 5.01, N 11.67.

3.6.3. 2-Methyl-5-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]pyridazin-3(2*H*)-one 8c. Purification by column chromatography on silica gel using AcOEt/hexane (1:3) as eluent. Mp 193–194 °C (MeOH). Yield 89%. IR (KBr): ν_{max}/cm^{-1} 1666 (CO), 1645 (CO), 1586 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 8.09 (d, $J=1.9$ Hz, 1H, H_6), 7.70 (m, 2H, aromatics), 7.31 (d, $J=15.5$ Hz, 1H, CH), 7.21–6.68 (m, 5H, 3H, aromatics, 1H, CH, 1H, H_4), 3.69 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 189.3, 160.8, 138.6, 137.6, 137.4, 134.3, 134.1, 129.3, 129.0, 128.6, 127.9, 40.5. MS (70 eV) *m/z* (%): 240 (M^+, 100), 211 (40). Anal. Calcd for $C_{14}H_{12}N_2O_2$, C 69.99, H 5.03, N 11.66; found, C 70.07, H 5.01, N 11.66.

X-ray structure analysis. Crystals of **8c** were grown by slow evaporation from a methanol solution. *Crystal data*. $C_{14}H_{12}N_2O_2$, $M=240.26$, triclinic, $a=5.5013(4)$ Å, $b=7.8346(5)$ Å, $c=13.6808(9)$ Å, $\alpha=87.116(6)°$, $\beta=86.082(6)°$, $\gamma=85.108(5)°$, $V=585.54(7)$ Å^3 [by least-squares refinement on diffractometer angles for 34 automatically centered reflections with $10.73<\theta<27.74°$, $\lambda=1.54178$ Å, $T=293(2)$ K], space group $P\bar{1}$, $Z=2$, $D_c=1.363(1)$ g cm^{-3}, $\mu=0.758$ mm^{-1}.

A prism-like colourless crystal ($0.46\times0.06\times0.02\ mm^3$) was used for the analysis. CCDC 231679 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

3.6.4. 2-Benzyl-5-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]pyridazin-3(2*H*)-one 8d. Purification by column chromatography on silica gel using AcOEt/hexane (1:8) as eluent. Mp 174–175 °C (isopropanol). Yield 70%. IR (KBr): ν_{max}/cm^{-1} 1646 (CO), 1629 (CO), 1578 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 8.15 (d, $J=2.0$ Hz, 1H, H_6), 7.92 (d, $J=8.2$ Hz, 2H, aromatics), 7.54 (d, $J=15.5$ Hz, 1H, CH), 7.42 (m, 5H, aromatics), 7.10 (m, 4H, 3H aromatics + H_4), 6.75 (d, $J=15.5$ Hz, 1H, CH), 5.01 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 189.3, 160.3, 138.5, 137.6, 137.4, 136.3, 134.7, 134.1, 129.3, 129.2, 129.1, 129.0, 128.6, 128.5, 128.4, 55.44. MS (70 eV) *m/z* (%): 316 (M^+, 72), 197 (58), 184 (100). Anal. Calcd for $C_{20}H_{16}N_2O_2$, C 75.93, H 5.10, N 8.86; found, C 75.95, H 5.09, N 8.85.

3.6.5. 2-Benzyl-5-(3-hydroxy-3-phenylprop-1-yn-1-yl)pyridazin-3(2*H*)-one 8e. This compound was obtained by following the general procedure described above for the Sonogashira alkynylation of compounds **3** but at room temperature. Careful work up and purification by column chromatography on silica gel using AcOEt/hexane (1:3) as eluent afforded **8e** (30%) and **8d** (67%). **8e**: Mp 133–134 °C (isopropanol). IR (KBr): ν_{max}/cm^{-1} 3254 (OH), 2218 (C–≡–C), 1645 (CO), 1581 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.64 (d, $J=1.9$ Hz, 1H, H_6), 7.53 (m, 2H, aromatics), 7.36–7.12 (m, 8H, aromatics), 6.96 (d, $J=1.9$ Hz, 1H, H_4), 5.65 (d, $J=6.0$ Hz, 1H, CH), 5.25 (s, 2H, CH_2), 3.72 (d, $J=6.0$ Hz, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 159.8, 139.9, 137.7, 136.1, 131.4, 129.2, 129.1, 129.0, 128.4, 128.0, 126.9, 90.0, 80.2, 65.0, 55.1, 31.3. MS (70 eV) *m/z* (%): 316 (M^+, 100), 91 (75). Anal. Calcd for $C_{20}H_{16}N_2O_2$, C 75.93, H 5.10, N 8.86; found, C 75.98, H 5.12, N 8.90.

Base-promoted isomerisation of intermediate **8e**. A mixture of 2-benzyl-5-(3-hydroxy-3-phenylprop-1-yn-1-yl)pyridazin-3(2*H*)-one **8e** (50 mg), MeOH (7 mL) and a catalytic amount of triethylamine was heated under reflux until the starting material had been completely transformed into the chalcone **8d**. The solvent was evaporated in vacuo and the resulting residue was purified by column chromatography on silica gel using AcOEt/hexane (1:8) as eluent. The compound obtained had identical physical and spectroscopic properties to **8d**. Mp 174–175 °C (isopropanol).

Compounds **11a–b** and **10a–c** were obtained by following the general procedures previously described for the Suzuki, Heck, Stille or Sonogashira reactions but starting from the 2-hydroxymethyl-5-iodopyridazin-3(2*H*)-one **3f**.

3.6.6. 5-Vinylpyridazin-3(2*H*)-one 10a. Purification by column chromatography on silica gel using AcOEt/hexane (1:3) as eluent. Mp 279–280 °C (dec) (isopropanol). Yield 65%. IR (KBr): ν_{max}/cm^{-1} 1664 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 12.30 (bs, 1H, NH), 7.93 (d, $J=1.8$ Hz, 1H, H_6), 6.77 (d, $J=1.8$ Hz, 1H, H_4), 6.50 (dd, $J=6.7$, 11.0 Hz, 1H, CH), 5.96 (d, $J=16.6$ Hz, 1H, CH), 5.62 (d, $J=11.0$ Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 163.0, 135.8, 131.8, 131.5, 125.4, 122.9. MS (70 eV) *m/z* (%): 122 (M^+, 84), 58 (100). HRMS *m/z* calcd for $C_6H_6N_2O$ (M^+): 122.0554, found: 122.0556.

3.6.7. 5-Phenylpyridazin-3(2*H*)-one 10b. Purification by column chromatography on silica gel using AcOEt/hexane (1:2) as eluent. Mp 193–194 °C (isopropanol). Yield 60%. IR (KBr): ν_{max}/cm^{-1} 1662 (CO), 1534 (aromatics). ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 13.10 (bs, 1H, NH), 8.29 (d, $J=2.1$ Hz, 1H, H_6), 7.83–7.78 (m, 2H, aromatics), 7.52–7.48 (m, 3H, aromatics), 7.11 (d, $J=2.1$ Hz, 1H, H_4). ^{13}C NMR (DMSO-d_6 75 MHz), δ (ppm): 162.3, 143.6, 136.2, 133.9, 130.6, 129.6, 127.5, 124.5. MS (70 eV) *m/z* (%): 172 (M^+, 100), 144 (45), 115 (85). Anal. Calcd for $C_{10}H_8N_2O$, C 69.76, H 4.68, N 16.27; found, C 69.77, H 4.89, N 16.34.

3.6.8. 5-(3-Hydroxyprop-1-yn-1-yl)pyridazin-3(2*H*)one 10c. Purification by column chromatography on silica gel using AcOEt/hexane (1:8) as eluent. Mp 179–180 °C (isopropanol). Yield 68%. IR (KBr): ν_{max}/cm^{-1} 3500–300 (NH), 2226 (C≡C), 1640 (CO). ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 13.14 (bs, 1H, NH), 7.79 (d, $J=1.9$ Hz, 1H, H_6), 6.91 (d, $J=1.9$ Hz, 1H, H_4), 5.51 (t, $J=5.44$ Hz, 1H, OH), 3.71 (d, $J=5.44$ Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.2, 137.4, 130.9, 128.5, 98.9, 78.8, 49.7. MS (70 eV) *m/z* (%): 150 (M^+, 100), 121 (85), 94 (50). Anal. Calcd for $C_7H_6N_2O$, C 56.00, H 4.03, N 18.66; found, C 56.13, H 4.11, N 18.72.

3.6.9. 5-[(1*E*)-3-Oxo-3-phenylprop-1-en-1-yl]pyridazin-3(2*H*)-one 10d. Purification by column chromatography on silica gel using AcOEt/hexane (1:2) as eluent. Mp 193–194 °C (MeOH). Yield 60%. IR (KBr): ν_{max}/cm^{-1} 1660 (CO), 1615 (CO), 1576 (aromatics). ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 13.42 (bs, 1H, NH),, 8.10 (d, $J=8.12$ Hz, 2H, aromatics), 8.01 (d, $J=1.9$ Hz, 1H, H_6), 7.53 (d, $J=15.5$ Hz, 1H, CH), 7.46 (m, 3H, aromatics), 7.28 (d, $J=15.5$ Hz, 1H, CH), 7.06 (d, $J=1.9$ Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 189.2, 161.5, 138.7, 137.7, 137.5, 134.4, 134.2, 129.4, 129.1, 128.7, 128.0. MS (70 eV) *m/z* (%): 226 (M^+, 100), 197 (84), 105 (48). Anal. Calcd for $C_{13}H_{10}N_2O_2$, C 69.02, H 4.46, N 12.38; found, C 69.11, H 4.42, N 12.48.

3.6.10. Methyl (2*E*)-3-(6-oxo-1,6-dihydropyridazin-4-yl)acrylate 10e. Purification by column chromatography on silica gel using AcOEt/hexane (1:1) as eluent. Mp 205–207 °C (MeOH). Yield 62%. IR (KBr): ν_{max}/cm^{-1} 1719 (COO), 1657 (CO). ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 13.07 (bs, 1H, NH), 8.27 (d, $J=1.8$ Hz, H_6), 7.45 (d, $J=16.2$ Hz, 1H, CH), 7.15 (d, $J=1.8$ Hz, H_4), 6.90 (d, $J=16.2$ Hz, 1H, CH), 3.34 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 166.0, 161.2, 139.0, 138.5, 135.1, 129.0, 125.3, 52.7. MS (70 eV) *m/z* (%): 180 (M^+, 100). Anal. Calcd for $C_8H_8N_2O_3$, C 53.33, H 4.48, N 15.55; found, C 53.42, H 4.56, N 15.56.

3.6.11. 2-Hydroxymethyl-5-vinylpyridazin-3(2*H*)-one 11a. Purification by column chromatography on silica gel using AcOEt/hexane (1:5) as eluent. Mp 91–93 °C (isopropanol). Yield 65%. IR (KBr): ν_{max}/cm^{-1} 1660 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.91 (d, $J=1.8$ Hz, 1H, H_6), 6.77 (d, $J=1.8$ Hz, 1H, H_4), 6.52 (dd, $J=6.7$, 11.0 Hz, 1H, CH), 5.97 (d, $J=16.6$ Hz, 1H, CH), 5.63 (d, $J=11.0$ Hz, 1H, CH), 5.52 (d, $J=6.1$ Hz, 2H, CH_2), 5.01 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 161.9, 141,9, 135.1, 131.5, 125.5, 123.0, 76.67. MS (70 eV) *m/z* (%): 152 (M^+, 42), 122 (100), 58 (52). HRMS *m/z* calcd for $C_7H_8N_2O_2$ (M^+): 152.0586, found: 152.0594.

3.6.12. 2-Hydroxymethyl-5-(3-hydroxyprop-1-yn-1-yl)pyridazin-3(2*H*)-one 11b. Purification by column chromatography on silica gel using AcOEt/hexane (1:8) as eluent. Mp 118–120 °C (isopropanol). Yield 70%. IR (KBr): ν_{max}/cm^{-1} 1640 (CO). ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 7.879 (d, $J=1.9$ Hz, 1H, H_6), 7.01 (d, $J=1.9$ Hz, 1H, H_4), 6.76 (t, $J=7.6$ Hz, 1H, OH), 5.52 (t, $J=5.1$ Hz, 1H, OH), 5.27 (d, $J=7.6$ Hz, 2H, CH_2) 4.34 (d, $J=5.1$ Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 159.1, 137.1, 131.0, 128.5, 98.7, 78.7, 73.9, 49.7. MS (70 eV) *m/z* (%): 180 (M^+, 76), 150 (100), 121 (55). HRMS *m/z* calcd for $C_8H_8N_2O_3$ (M^+): 180.0535, found: 180.0551.

Acknowledgements

Financial support from the Xunta de Galicia (Project PGIDT 01PX20309PR) is gratefully acknowledged. We are also grateful to Professor Bert Maes for valuable discussions and suggestions.

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