Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2477–2484

TETRAHEDRON

Pyridazine derivatives. Part 33:☆ Sonogashira approaches in the synthesis of 5-substituted-6-phenyl-3(2*H*)-pyridazinones

Alberto Coelho, Eddy Sotelo and Enrique Raviña*

Departamento de Química Orgánica, Laboratorio de Química Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, Santiago de Compostela 15782, Spain

Received 26 November 2002; revised 17 February 2003; accepted 17 February 2003

Abstract—Several 6-phenyl-3(2*H*)-pyridazinones bearing different alkynyl groups at position 5 have been prepared by a palladium-catalysed Sonogashira cross-coupling reaction. An interesting base-promoted electronically permitted isomerization has been observed during the coupling of 1-phenyl-2-propyn-1-ol. This rearrangement afforded the *E*-chalcone **6** in excellent yield.

1. Introduction

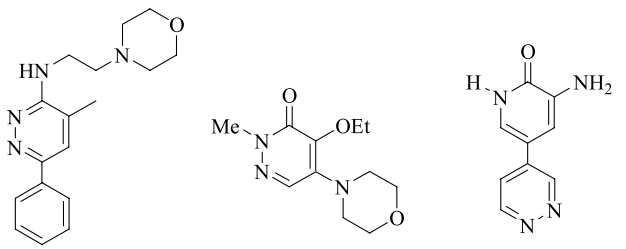
The interesting pharmacological activity displayed by pyridazine derivatives has been demonstrated in recent years not only by the growing number of papers and patents describing them but also by the development of several pyridazine-based drugs and pharmacological tools (Fig. 1). Pyridazinones initially received special attention in the search for drugs acting on the cardiovascular system[2] and as agrochemicals,[3] but more recent publications have dealt with the wide range of biological actions associated with these compounds.[4]

Despite the usefulness of pyridazines, simple methods for the introduction of a range of substituents into this six-membered heterocycle have not yet been extensively developed and, for this reason, new advances in this area continue to be of interest. Among the synthetic methods described in the recent literature, transition metal mediated cross-couplings have proven to be a powerful route for mild, highly efficient carbon–carbon bond formation. In particular, processes involving palladium(0) catalysis are extremely useful for the synthesis of a diverse range of molecules owing to the excellent levels of selectivity and high functional group compatibility. In this respect, palladium cross-coupling reactions have become an important tool in the synthesis of pyridazine derivatives.[5]

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.[6] An example of this phenomenon can be seen in the significant modification in the coupling behaviour (due to the differences in acidity) between halopyridazines and halo-3(2*H*)-pyridazinones.[7] These reactivity differences have allowed the use of 2-blocked-3-pyridazinones as starting materials in palladium-catalysed transformations and have also stimulated the search for new and efficient protecting groups in this area.[7,8]

As part of our medicinal chemistry program aimed at the search for novel pyridazinone-based antiplatelet agents,[9] it became of interest to prepare several 5-alkynyl derivatives **II** (structurally related to the previously prepared 5-substituted-6-phenyl-3(2H)-pyridazinones **I**), which were required for structure–activity relationship (SAR) studies (Fig. 2).

The most obvious synthetic strategy to prepare compounds **II** involves the palladium-mediated cross-coupling transformation of terminal acetylenes with the appropriately



MINAPRINE (Antidepressant) **EMORFAZONE** (Antiinflammatory) **AZANRINONE** (Cardiotonic)

Figure 1. Several pharmacologically useful pyridazine derivatives.

☆ See Ref. 1.

Keywords: pyridazinones; Sonogashira coupling; chalcone.

* Corresponding author. Fax: +34-981-594912; e-mail: qofara@usc.es

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00263-1

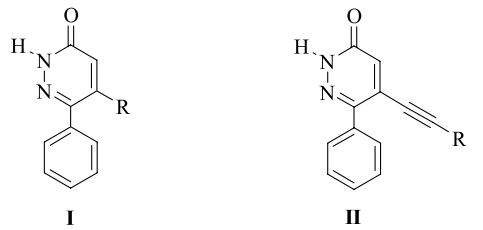
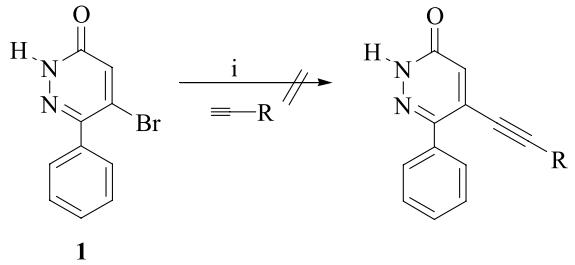


Figure 2.



Scheme 1. (i) $Pd(PPh_3)_2Cl_2/CuI/Et_3N/DMF/60°C$.

substituted 5-halo-3(2*H*)-pyridazinone using the well-documented Sonogashira reaction.[10] There are several references describing the Sonogashira reaction on halo-pyridazines[11] but, to the best of our knowledge, there are only two reports describing such a transformation on 3(2*H*)-pyridazinones. The first report on the palladium-catalysed Sonogashira synthesis of pyridazinones bearing alkynyl groups was published by our group.[12] More recently, Lemière and co-workers described the preparation of symmetrically and unsymmetrically 4,5-substituted alkynyl pyridazinones.[13] As a continuation of our search for new, simple and efficient palladium-catalysed procedures to allow the pharmacomodulation of the 5 position of 6-phenyl-3(2*H*)-pyridazinone system, here we describe results obtained by applying the Sonogashira reaction.

In the initial experiment 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1**[14] was used as the starting material (Scheme 1). In a similar way to our previous studies on Suzuki arylation of this system,[7] all attempts to perform the cross-coupling reactions between **1** and terminal acetylenes under Sonogashira conditions afforded only around 5–10% of the expected coupling products and more than 85% of **1** was recovered.

The low reactivity of this system can be attributed to the acidity of the NH group, or rather to the lactam function in the pyridazinone ring (which is about as acidic as phenol $PK_a \approx 10$). In a subsequent reaction the NH group of **1** was protected with the methoxymethyl (MOM) group (Scheme 2), which can be easily removed by treatment of the corresponding 2-methoxymethyl-3-pyridazinone either with 6N hydrochloric acid or a Lewis acid (see Section 2).

Several experiments were performed using the cross-coupling reaction of **2** with TMS-acetylene as model. A brief screen of Pd(0) sources showed that $Pd(PPh_3)_2Cl_2$ was the best choice (Table 1). As can be seen from the results in Table 1, which summarise some of the conditions tested, the efficiency of the coupling reaction was highly dependent upon the type of solvent used. DMF and dioxane proved to be much better than THF, DCM or MeCN.

After some optimisation of the experimental conditions it was found that alkynyl coupling of **2** can be readily achieved, in moderate to excellent yields (Table 2), using bis(triphenylphosphine)palladium chloride as the palladium source, copper(I) iodide as a co-catalyst, triethylamine as a base and DMF as a solvent (Scheme 2). Under these conditions, reactions occurred cleanly and rapidly at temperatures up to 55°C and very little starting halide remained after five hours in all cases. The coupling process is free of side reactions, such as alkyne homocoupling, which indicates that under these conditions carbon–carbon bond formation is significantly faster than homocoupling. The products were obtained with 80–90% purity after a simple work-up and these materials were further purified by column chromatography.

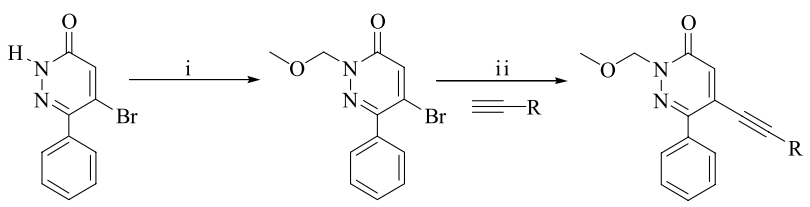
Once the coupling reactions had been successfully carried out, the methoxymethyl (MOM) group was removed from compounds **3a–g**. Our previous studies in this area have shown that the use of hydrochloric acid is not tolerated by the sensitive functionalities present on **3**[8a] and so the MOM deprotection of acid sensitive compounds was achieved using the milder Lewis acid aluminium chloride.

Curiously, despite the fact that this method appears to be

Table 1. Sonogashira couplings with various catalytic systems

Catalyst system	Solvent	Yields (%)
$Pd(PPh_3)_4/CuI/Et_3N$	CH_3CN	39
$Pd(PPh_3)_4/CuI/Et_3N$	DMF	45
$Pd(PPh_3)_2Cl_2/CuI/Et_3N$	Dioxane	70
$Pd(PPh_3)_2Cl_2/CuI/Et_3N$	DCM	51
$Pd(PPh_3)_2Cl_2/CuIEt_3N$	CH_3CN	63
$Pd(PPh_3)_2Cl_2/CuI/Et_3N$	DMF	90

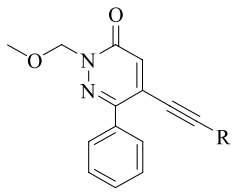
All coupling reactions were conducted at 55°C with 1.2 equiv. of alkyne, 10% $Pd(PPh_3)_2Cl_2$, 10% CuI, 2 equiv. of amine, solvent.



i) $Cl–CH_2OCH_3/CH_2Cl_2/DMAP$ ii) $Pd(PPh_3)_2Cl_2/CuI/Et_3N/DMF/60$ °C

Scheme 2. Palladium-mediated alkynylation of **2**.

Table 2. Sonogashira cross-coupling reaction on **2**



3a-g

Entry	R	Yield (%)	Time (h)
3a	CH_2OH	85	6
3b	CH_2CH_2OH	90	4
3c	Ph	80	6
3d	TMS	90	3
3e	H	60[a]	–
3f	$CHOHCH_3$	78	5
3g	CH_2OCOCH_3	72[b]	–

[a] Overall yield (Sonogashira-coupling+desilylation) from bromopyridazinone **2**.
[b] Overall yield (Sonogashira-coupling+acetylation) from bromopyridazinone **2**.

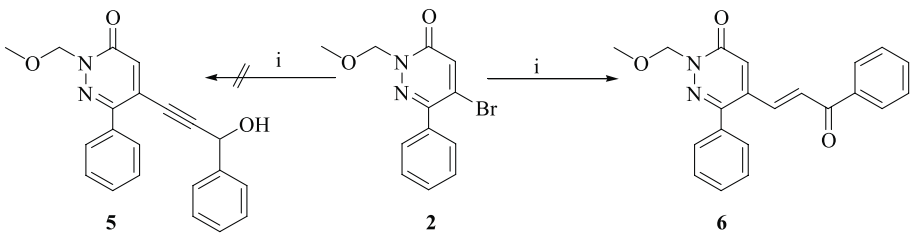
quite general, it failed in the cross-coupling reaction of **2** with 1-phenyl-2-propyn-1-ol (Scheme 3). Thus, heating a mixture of **2** and 1-phenyl-2-propyn-1-ol under the aforementioned conditions did not give the expected 5-(3-hydroxy-3-phenylprop-1-ynyl)-2-methoxymethyl-6-phenyl-3-pyridazinone **5** but that the isomeric *E*-chalcone **6** was obtained in good yield (80%).

The identity of *E*-5-(3-oxo-3-phenylpropenyl)-2-methoxymethyl-6-phenyl-3-pyridazinone (**6**) was unambiguously established on the basis of the analytical and spectroscopic data (see Section 2). The ^{1}H NMR spectra of product **6** contained two doublets centred, respectively, at 8.03 and 7.23 ppm with a coupling constant of 15.5 Hz, which confirms a *trans* stereochemistry for the double bond. The observation of signals corresponding to a ketonic carbonyl function in the ^{13}C NMR and IR spectra at 189.0 ppm and 1700 cm^{-1}, respectively, confirmed the existence of the ketone.

The unusual formation of chalcone **6** is not dissimilar to results described in previous papers concerning the Sonogashira coupling of several halides with 1-phenyl-2-propyn-1-ol[15–20] or some transition metal-catalysed redox isomerizations of propargyl alcohols to α,β-unsaturated carbonyl compounds.[21–23] This situation prompted a more detailed study of this transformation.

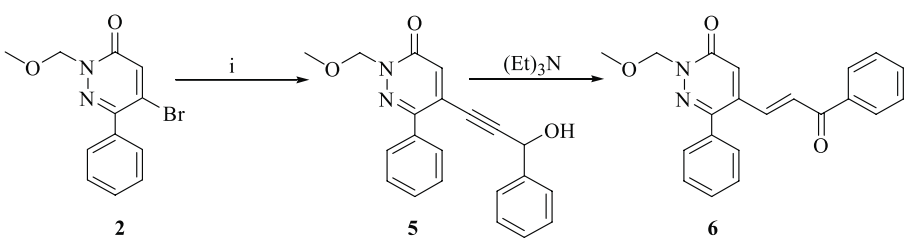
An exhaustive review of different reaction conditions enabled the isolation of the expected phenyl-substituted propargyl alcohol **5** by carrying out the reaction at room temperature (25°C) (Scheme 4). Identification of intermediate **5** is supported by both analytical and spectroscopic data (see Section 2); a small sharp absorption at 2226 cm^{-1} in the IR spectrum and signals corresponding to the alkyne unit (81.9, 101.0 ppm) in the ^{13}C NMR spectrum. The fact that compound **5** is the main intermediate during chalcone formation has also been demonstrated by quantitative formation of **6** after stirring **5** in presence of triethylamine in a range of solvents (DCM, MeOH, THF, DMF)—even at room temperature.

It is worth noting that this reaction produces the chalcone **6** with an *E*-selectivity greater than 95% after isolation and purification by column chromatography. The exclusive formation of the trans olefin can be understood in terms of the severe steric interaction between the phenyl group at position 5 of the heterocyclic ring and the carbonyl moiety in the *Z* isomer.



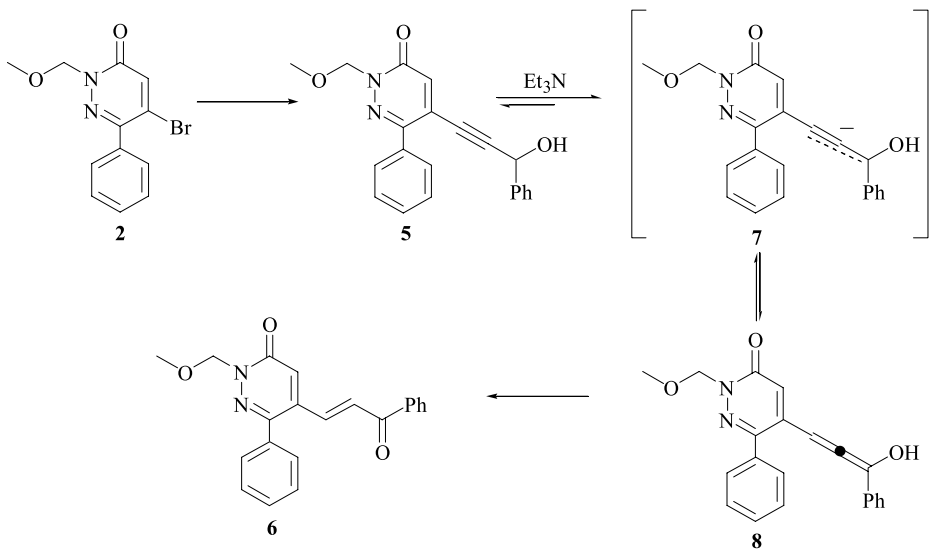
i) ≡–CH(OH)Ph, $Pd(PPh_3)_2Cl_2$/CuI/Et_3N/DMF/55 °C/12 h.

Scheme 3. Sonogashira cross-coupling of 1-phenyl-2-propyn-1-ol with **2**.



i) ≡–CH(OH)Ph, $Pd(PPh_3)_2Cl_2$/CuI/Et_3N/DMF/r. t./2 h

Scheme 4. Base-promoted isomerization of **5**.



Scheme 5. Mechanistic proposal for the formation of chalcone **6**.

On the evidence of this data the explanation given for a similar transformation on pyrimidines[15–17] (which is based on a co-ordination of an intermediate during a hydropalladation–dehydropalladation catalytic cycle to the heterocyclic nitrogen) is not applicable in this case due to the absence of heteroatom co-ordination in pyridazinones. Our results are, however, consistent with more recent works[19,20] indicating that the reaction is not only limited to compounds containing iodine as the halogen[18] and they confirm that the formation of **6** occurs exclusively in a base-catalysed manner—the isomerization process being facilitated by the electron-deficient nature of the pyridazinone system.

The mechanistic pathway proposed for this transformation is outlined in Scheme 5. Sonogashira coupling of **2** with 1-phenyl-2-propyn-1-ol affords the substituted propargyl alcohol **5** which, upon deprotonation at the propargyl centre with triethylamine, leads to a propargyl-allenyl anion **7**. Protonation of this species afforded the allene **8**. Finally, the allenol-enone tautomerism furnishes the *trans*-configured enone **6**.

In summary, we have prepared several 5-alkenyl-6-phenyl-3(2*H*)-pyridazinones by using the Sonogashira cross-coupling reaction of **2** with different acetylenes. The palladium-mediated alkynylation of **2** using 1-phenyl-2-propyn-1-ol afforded the isomeric *E*-chalcone **6** in excellent yield. Our detailed study of this transformation leads to the conclusion that the key factor in the isomerization step is the electron-deficient nature of the starting halide.

2. 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. 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.

2.1. Synthesis of 5-alkynyl-6-phenyl-2-methoxymethyl-3-pyridazinones 3a–g. General procedure

To a degassed (argon) suspension of bromopyridazinone **2** (1.02 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol) and CuI (0.01 mmol) in DMF (15 mL) was added the corresponding alkyne (1.52 mmol) and triethylamine (2.032 mmol). The mixture was heated at 55°C under argon until the starting material had been consumed (during this time the solution turned dark brown). The mixture was cooled to room temperature, diluted with dichloromethane and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel. Further purification was carried out by recrystallization.

2.1.1. 5-(3-Hydroxyprop-1-ynyl)-2-methoxymethyl-6-phenyl-3-pyridazinone (3a). Purification by column chromatography on silica gel using AcOEt/hexane (3:1) as eluent afford a pale yellow oil; yield 85%. IR (KBr): ν_{max}/cm^{-1} 3054 (OH), 2305 (C≡C), 1663 (CO), 1559 (Aromatics), 1097 (C–O–C). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.69 (m, 2H, Aromatics), 7.43 (m, 3H, Aromatics), 7.15 (s, 1H, H_4), 5.43 (s, 2H, O–CH_2), 5.37 (s, 2H, –CH_2–), 3.45 (s, 3H, CH_3–O), 3.37 (brs, 1H, OH). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.0, 146.6, 134.5, 133.4, 130.0, 129.1, 129.1, 128.5, 100.9, 82.1, 80.0, 58.2, 51.4. MS (70 eV) *m/z* (%): 270 (M^+, 10), 240 (56), 227 (54), 139 (50), 115 (100).

2.1.2. 5-(4-Hydroxybut-1-ynyl)-2-methoxymethyl-6-phenyl-3-pyridazinone (3b). Purification by column chromatography on silica gel using AcOEt/hexane (3:1) as eluent afford a pale yellow oil; yield 90%. IR (KBr): ν_{max}/cm^{-1} 3438 (OH), 2229 (C≡C), 1649 (CO), 1567 (Aromatics), 1098 (C–O–C). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.69 (m, 2H, Aromatics), 7.44 (m, 3H, Aromatics), 7.07 (s, 1H, H_4), 5.46 (s, 2H, O–CH_2), 3.67 (t, J=6.2 Hz, –CH_2–), 3.49 (s, 3H, CH_3–O), 2.60 (t, J=6.2 Hz, –CH_2–), 3.39 (brs, 1H, OH). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.0, 146.4, 133.0, 135.0, 129.9, 129.1, 128.4, 100.4, 81.9, 77.0, 60.7, 58.2, 30.0, 24.4. MS (70 eV) *m/z* (%): 284 (M^+, 19), 254 (100), 253 (68), 241 (79), 183 (46), 152 (61).

2.1.3. 2-Methoxymethyl-6-phenyl-5-(2-phenylethynyl)-3-pyridazinone (3c). Purification by column chromatography on silica gel using AcOEt/hexane (1:4) as eluent gave a colourless oil; yield 80%. IR (KBr): ν_{max}/cm^{-1} 2212 (C≡C), 1671 (CO), 1585 (Aromatics), 1080 (C–O–C). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.80 (m, 2H, Aromatics), 7.54 (m, 1H, Aromatics), 7.44 (m, 3H, Aromatics), 7.35 (m, 4H, Aromatics), 7.17 (s, 1H, H_4), 5.50 (s, 2H, –CH_2O), 3.52 (s, 3H, –OCH_3). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 159.9, 146.4, 134.9, 132.5, 132.3, 130.4, 130.0, 129.9, 129.2, 128.9, 128.4, 121.6, 101.1, 84.6, 81.9, 58.3. MS (70 eV) *m/z* (%): 316 (M^+, 15), 286 (59), 273 (46), 215 (100), 126 (32).

2.1.4. 2-Methoxymethyl-6-phenyl-5-(3-trimethylsilanylethynyl)-3-pyridazinone (3d). Purification by column chromatography on silica gel using AcOEt/hexane (1:3) as eluent afford a yellow oil; yield 75%. IR (KBr): ν_{max}/cm^{-1} 2162 (C≡C), 1670 (CO), 1586 (Aromatics), 1090 (C–O–C). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.69 (m, 2H, Aromatics), 7.42 (m, 3H, Aromatics), 7.05 (s, 1H, H_4), 5.46 (s, 1H, CH_2O), 3.51 (s, 3H, –OCH_3), 0.12 (s, 9H, 3×CH_3). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 159.7, 146.2, 134.6, 133.6, 129.7, 129.2, 129.0, 128.2, 108.7, 99.1, 81.8, 58.1, −0.4. MS (70 eV) *m/z* (%): 312 (M^+, 23), 282 (94), 269 (100), 211 (51), 107 (57).

2.1.5. 5-Ethynyl-2-methoxymethyl-6-phenyl-3-pyridazinone (3e). This compound was prepared by desilylation of **3d**. A solution of compound **3d** (100 mg, 0.320 mmol) in 1 M methanolic KOH (4 mL) was stirred at room temperature during 15 min. The mixture was acidified to pH 7 with 3N HCl and the organic material was extracted with dichloromethane and dried with anhydrous Na_2SO_4. Purification by column chromatography using AcOEt/hexane (1:2) furnished a colourless oil; yield 53 mg (70%). IR (KBr): ν_{max}/cm^{-1} 2105 (C≡C), 1669 (CO), 1585 (Aromatics), 1084 (C–O–C). ^1H NMR ($CDCl_3$ 75 MHz), δ (ppm): 7.73 (m, 2H, Aromatics), 7.42 (m, 3H, Aromatics), 7.19 (s, 1H, H_4), 5.48 (s, 2H, CH_2), 3.50 (s, 3H, CH_3), 3.48 (s, 1H, CH). ^{13}C NMR ($CDCl_3$ 300 MHz), δ (ppm): 159.5, 146.3, 135.1, 134.5, 129.9, 129.1, 128.5, 128.3, 89.3, 82.0, 78.2, 58.3. MS (70 eV) *m/z* (%): 240 (M^+, 7), 210 (33), 197 (25), 139 (51), 118 (14), 77 (12), 58 (100).

2.1.6. 5-(3-Hydroxybut-1-ynyl)-2-methoxymethyl-6-phenyl-3-pyridazinone (3f). Purification by column chromatography on silica gel using AcOEt/hexane (3:1) as eluent afforded a yellow oil; yield 78%. IR (KBr): ν_{max}/cm^{-1} 2224 (C≡C), 1654 (CO), 1584 (Aromatics), 1094 (C–O–C). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.67 (m, 2H, Aromatics), 7.41 (m, 3H, Aromatics), 7.12 (s, 1H, H_4), 5.41 (s, 2H, CH_2), 4.60 (d, J=6.6 Hz, 1H, CH), 3.78 (brs, 1H, OH), 3.43 (s, 3H, CH_3), 1.39 (d, J=6.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.0, 146.7, 134.5, 133.1, 129.9, 129.2, 129.1, 128.4, 104.3, 82.0, 78.6, 58.6, 58.2, 23.6. MS (70 eV) *m/z* (%): 284 (M^+, 16), 254 (100), 241 (100), 139 (86), 115 (44), 76 (65), 57 (77).

2.1.7. 5-(3-Acetoxyprop-1-ynyl)-2-methoxymethyl-6-phenyl-3-pyridazinone (3g). This compound was prepared by acetylation of **3a**. To a solution of compound **3a** (200 mg, 0.74 mmol) in pyridine (4.5 mL) was added acetic anhydride (2 mL, 2.22 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was evaporated in vacuo and the oily residue was precipitated with 30 mL of ice containing 20 mL of 10% HCl. The product was extracted with ethyl acetate, the organic phase was dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The resulting oily residue was purified by column chromatography on silica gel using AcOEt/hexane (1:1) as eluent to afford a yellow oil, which crystallised on standing to give white needles; yield 85%. Mp 68–69°C. IR (KBr): ν_{max}/cm^{-1} 2338 (C≡C), 1748 (CO), 1669 (CO), 1587 (Aromatics), 1096 (C–O–C). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.68 (m, 2H, Aromatics), 7.42 (m, 3H, Aromatics), 7.10 (s, 1H, H_4), 5.45 (s, 2H, O–CH_2), 4.77 (s, 2H, –CH_2–), 3.48 (s, 3H, CH_3–O), 2.05 (s, 3H, –$COCH_3$). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 170.2, 159.5, 146.0, 134.5, 133.9, 129.8, 129.1, 128.4, 128.3, 95.2, 82.0, 81.1, 58.2, 52.4, 20.9. MS (70 eV) *m/z* (%): 312 (M^+, 20), 282 (100), 269 (73), 151 (57), 115 (17), 77 (13).

2.1.8. 5-(3-Hydroxy-3-phenyl-prop-1-ynyl)-2-methoxymethyl-6-phenyl-3-pyridazinone (5). This intermediate can be isolated by performing the cross-coupling reaction at room temperature (25°C) (2 h) and following the course of the reaction by TLC. The solvent was removed in vacuo at room temperature and the resulting oily residue contained a mixture of the starting material **2**, the alkyne **5** and the chalcone **6**. This mixture was separated by column chromatography on silica gel using AcOEt/hexane (1:4) as eluent to afford 15% of **2**, 50% of chalcone **6** and 30% of the intermediate **5** as a yellow oil. IR (KBr): ν_{max}/cm^{-1} 3352 (OH), 2226 (C≡C), 1656 (CO), 1584 (Aromatics), 1094 (C–O–C). ^1H NMR ($CDCl_3$ 75 MHz), δ (ppm): 7.65 (m, 2H, Aromatics), 7.34 (m, 8H, Aromatics), 7.16 (s, 1H, H_4), 5.58 (s, 1H, CH), 5.46 (s, 2H, CH_2), 3.49 (s, 1H, OH), 3.48 (s, 1H, CH_3). ^{13}C NMR ($CDCl_3$ 300 MHz), δ (ppm): 159.8, 145.4, 139.5, 133.7, 130.3, 129.8, 129.3, 129.1, 129.1, 128.7, 128.5, 126.9, 101.0, 82.0, 81.9, 65.2, 58.2. MS (70 eV) *m/z* (%): 346 (M^+, 38), 316 (100), 303 (71), 215 (30), 202 (17), 77 (11). HRMS, *m/z*: calcd for $C_{21}H_{18}N_2O_3$ (M^+) 346.3793, found 346.3897.

2.1.9. 2-Methoxymethyl-5-(3-oxo-3-phenylpropenyl)-6-phenyl-3-pyridazinone (6). Column chromatography on silica gel using AcOEt/hexane (1:2) as eluent to give a white solid; yield 80%. Mp 177–178°C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 1700 (CO), 1662 (CO), 1588 (Aromatics), 1091 (C–O–C). ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 8.11 (m, 2H, Aromatics), 8.03 (d, J=15.5 Hz, 1H, CH), 7.63 (m,

8H, Aromatics), 7.51 (s, 1H, H_4), 7.23 (d, J=15.5 Hz, 1H, CH), 5.38 (s, 2H, CH_2), 3.37 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6 75 MHz), δ (ppm): 189.0, 159.9, 146.7, 139.5, 137.2, 137.0, 134.7, 134.1, 129.6, 129.5, 129.4, 129.2, 129.1, 128.9, 127.2, 81.0, 57.4. MS (70 eV) *m/z* (%): 346 (M^+, 45), 315 (67), 287 (29), 245 (15), 105 (13). Anal. calcd for $C_{21}H_{18}N_2O_3$ C 72.82, H 5.24, N 8.09; found, C 72.86, H 5.26, N 8.12.

2.2. Base-promoted isomerization of intermediate 5 under basic conditions

A mixture of 5-(3-Hydroxy-3-phenyl-prop-1-ynyl)-2-methoxymethyl-6-phenyl-3-pyridazinone **5** (60 mg), MeOH (7 mL) and a catalytic amount of triethylamine was heated under reflux until the starting material had been completely transformed in the chalcone **6**. The solvent was evaporated in vacuo, the resulting residue was purified by column chromatography on silica gel under the experimental conditions above described.

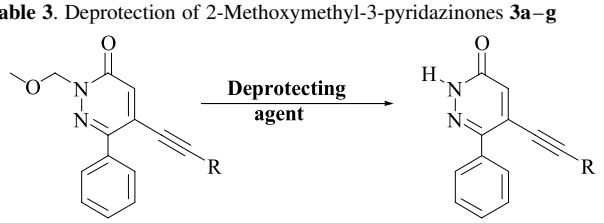
2.3. Representative procedure for the deprotection of 2-methoxymethyl-3-pyridazinones. Method A (6N HCl)

A mixture of the corresponding 2-methoxymethyl-3-pyridazinone **3** (1.11 mmol), MeOH (5 mL) and 6N HCl (15 mL) was heated under reflux until the starting material had been completely consumed (24–48 h). The mixture was extracted with dichloromethane, the organic layer dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel and then crystallised.

2.4. Representative procedure for the deprotection of 2-methoxymethyl-3-pyridazinones. Method B ($AlCl_3$)

In a carefully purged flask, $AlCl_3$ (670 mg, 5.03 mmol) was suspended in dry toluene (8 mL) and the mixture was stirred at room temperature during 10 min. The corresponding 2-methoxymethyl-3-pyridazinone **3** (1.00 mmol) in toluene (3 mL) was added dropwise and the mixture was heated under reflux for 1 h. Once the starting material had been consumed, 50 mL of ice was added and the mixture was stirred for 30 min. The mixture was extracted with chloroform and the organic layer dried with anhydrous Na_2SO_4. The solvent was removed in vacuo and the resulting solid was washed with ether, purified by column chromatography on silica gel and then recrystallized (Table 3).

Table 3. Deprotection of 2-Methoxymethyl-3-pyridazinones **3a–g**



3a-g **4a-g**

Entry	R	Yield(%)	Deprotecting agent
4a	CH_2OH	70	$AlCl_3$
4b	CH_2CH_2OH	78	HCl
4c	Ph	80	HCl
4d	TMS	85	HCl
4e	H	51	$AlCl_3$
4f	$CHOHCH_3$	80	$AlCl_3$
4g	CH_2OCOCH_3	85	$AlCl_3$

2.4.1. 5-(3-Hydroxyprop-1-ynyl)-6-phenyl-3(2*H*)-pyridazinone (4a). *Method B*. Purification by column chromatography on silica gel (AcOEt/hexane 1:5) gave white crystals; yield 80%. Mp 167–169°C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 3566 (OH), 2237 (C≡C), 1654 (CO), 1558 (Aromatics), 1098 (C–O–C). ^{1}H NMR (MeOD 300 MHz), δ (ppm): 11.33 (1H, brs, NH), 7.73 (m, 2H, Aromatics), 7.48 (m, 3H, Aromatics), 7.16 (s, 1H, H_4), 4.35 (s, 2H, $-CH_2$), 3.34 (bs, 1H, OH). ^{13}C NMR (MeOD 75 MHz), δ (ppm): 162.6, 148.9, 136.3, 133.7, 131.1, 130.8, 130.2, 129.5, 101.9, 80.6, 51.4. MS (70 eV) *m/z* (%): 226 (M^+, 60), 208 (100), 152 (62), 115 (61). Anal. calcd for $C_{13}H_{10}N_2O_2$, C 69.02, H 4.46, N 12.38; found, C 69.12, H 4.42, N 12.43.

2.4.2. 5-(4-Hydroxybut-1-ynyl)-6-phenyl-3(2*H*)-pyridazinone (4b). *Method A*. Purification by column chromatography on silica gel (AcOEt/hexane 1:5) gave white crystals; yield 80%. Mp 199–201°C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 3566 (OH), 2226 (C≡C), 1652 (CO), 1558 (Aromatics). ^{1}H NMR ($CDCl_3$ 300 MHz), δ (ppm): 10.91 (1H, brs, NH deuterium oxide exchangeable), 7.67 (m, 2H, Aromatics), 7.43 (m, 3H, Aromatics), 7.08 (s, 1H, H_4), 3.67 (t, J=6.2 Hz, 2H, $-CH_2-$), 2.62 (t, J=6.2 Hz, 2H, CH_2), 1.48 (brs, 1H, OH). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 159.6, 145.6, 135.0, 132.3, 129.3, 128.9, 128.8, 128.2, 100.9, 77.0, 59.3, 23.8. MS (70 eV) *m/z* (%): 240 (M^+, 60), 209 (51), 181 (64), 152 (100), 77 (43). Anal. calcd for $C_{14}H_{12}N_2O_2$, C 69.99, H 5.03, N 11.66; found, C 70.05, H 5.03, N 11.71.

2.4.3. 6-Phenyl-5-(2-phenylethynyl)-3(2*H*)-pyridazinone (4c). *Method A*. Purification by column chromatography on silica gel (AcOEt/hexane 1:5) gave a white solid; yield 80%. Mp 158–150°C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 1651 (CO), 1577 (Aromatics). ^{1}H NMR ($CDCl_3$ 300 MHz), δ (ppm): 11.25 (1H, brs, NH deuterium oxide exchangeable), 7.78 (m, 2H, Aromatics), 7.49 (m, 3H, Aromatics), 7.36 (m, 5H, Aromatics), 7.19 (s, 1H, H_4). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.7, 147.4, 134.9, 132.3, 132.2, 130.4, 130.1, 129.8, 129.2, 128.9, 128.4, 121.7, 101.2, 84.8. MS (70 eV) *m/z* (%): 272 (M^+, 100), 271 (40), 215 (40). Anal. calcd for $C_{18}H_{12}N_2O$, C 79.39, H 4.44, N 10.29; found, C 79.44, H 4.49, N 10.30.

2.4.4. 6-Phenyl-5-(3-trimethylsilanylethynyl)-3(2*H*)-pyridazinone (4d). *Method A*. Purification by column chromatography on silica gel (AcOEt/hexane 1:3) gave a white solid; yield 85%. Mp 156–157°C (Isopropanol). IR 2855 (NH), 2136 (C≡C), 1654 (CO), 1525 (Aromatics), 1133 (C–O–C). ^{1}H NMR ($CDCl_3$ 300 MHz), δ (ppm): 12.46 (1H, brs, NH deuterium oxide exchangeable), 7.73 (m, 2H, Aromatics), 7.42 (m, 3H, Aromatics), 7.13 (s, 1H, H_4), 0.16 (s, 9H, 3×CH_3). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 161.2, 147.4, 134.7, 133.1, 129.7, 129.2, 128.2, 108.9, 99.3, −0.4. MS (70 eV) *m/z* (%): 268 (M^+, 100), 253 (94), 225 (24), 139 (26), 107 (28), 77 (60). Anal. calcd for

$C_{15}H_{16}N_2OSi$, C 67.13, H 6.01, N 10.44; found, C 67.15, H 6.04, N 10.45.

2.4.5. 5-Ethynyl-6-phenyl-3(2*H*)-pyridazinone (4e). A solution of compound **4d** (100 mg, 301 mmol) in 1 M methanolic KOH (4 mL) was stirred at room temperature during 10 min. The mixture was acidified to pH 7 with 3N HCL and then extracted with dichloromethane to give a yellow solid. Further purification by column chromatography (AcOEt/hexane 1:1.5) and recrystallization from isopropanol furnished a white solid; yield 51%. Mp 202–203°C. IR (KBr): ν_{max}/cm^{-1} 2984 (NH), 2113 (C≡C), 1684 (CO), 1560 (Aromatics). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm): 13.35 (1H, brs, NH deuterium oxide exchangeable), 7.64 (m, 2H, Aromatics), 7.45 (m, 3H, Aromatics), 7.18 (s, 1H, H_4), 4.79 (s, 1H, CH), 3.37 (s, 9H, 3×CH_3). ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm): 159.4, 145.5, 134.9, 134.1, 129.4, 128.8, 128.3, 127.7, 91.8, 78.7. MS (70 eV) *m/z* (%): 196 (M^+, 66), 139 (38), 69 (41), 63 (51), 57 (100), 58 (93). Anal. calcd for $C_{12}H_8N_2O$, C 73.46, H 4.11, N 14.28; found, C 73.52, H 4.14, N 14.31.

2.4.6. 5-(3-Hydroxy-but-1-ynyl)-6-phenyl-3(2*H*)-pyridazinone (4f). *Method B*. Purification by column chromatography on silica gel (AcOEt/hexane 2:1) gave a white solid; yield 80%. Mp 178–180°C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 2926 (NH), 2230 (C≡C), 1652 (CO), 1585 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 12.25 (1H, brs, NH deuterium oxide exchangeable), 7.67 (m, 2H, Aromatics), 7.41 (m, 3H, Aromatics), 7.12 (s, 1H, H_4), 4.61 (q, J=6.6 Hz, 1H, CH), 3.45 (bs, 1H, OH), 1.40 (d, J=6.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.0, 146.7, 134.6, 132.8, 129.8, 129.3, 129.1, 128.4, 103.8, 79.0, 58.7, 23.6. MS (70 eV) *m/z* (%): 240 (M^+, 35), 197 (30), 165 (82), 139 (100), 115 (61), 77 (84), 51 (100). Anal. calcd for $C_{14}H_{12}N_2O_2$, C 69.99, H 5.03, N 11.66; found, C 70.09, H 5.12, N 11.87.

2.4.7. 5-(3-Acetoxyprop-1-ynyl)-6-phenyl-3(2*H*)-pyridazinone (4g). *Method B*. Purification by column chromatography on silica gel (AcOEt/hexane 2:1) gave a white solid; yield 70%. Mp 132–133°C. IR (KBr): ν_{max}/cm^{-1} 2332 (C≡C), 1744 (CO), 1681 (CO), 1558 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 12.69 (1H, brs, NH deuterium oxide exchangeable), 7.69 (m, 2H, Aromatics), 7.42 (m, 3H, Aromatics), 7.15 (s, 1H, H_4), 4.78 (s, 2H, $-CH_2-$), 2.07 (s, 3H, $-COCH_3$). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 170.3, 161.2, 147.1, 134.6, 133.4, 129.8, 129.1, 129.0, 128.4, 95.2, 81.4, 52.4, 20.9. MS (70 eV) *m/z* (%): 268 (M^+, 32), 225 (26), 208 (100), 152 (77), 126 (17), 77 (10). Anal. calcd for $C_{15}H_{12}N_2O_3$, C 67.16, H 4.51, N 10.44; found, C 67.18, H 4.55, N 10.44.

2.4.8. 5-(3-Oxo-3-phenyl-propenyl)-6-phenyl-3(2*H*)-pyridazinone (6a). *Method A*. Purification by column chromatography on silica gel (AcOEt/hexane 2:1) gave a white solid; yield 87%. Mp 230–231°C. IR (KBr): ν_{max}/cm^{-1} 1698 (CO), 1661 (CO), 1576 (Aromatics) mp 231–232°C. ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 11.77 (1H, brs, NH deuterium oxide exchangeable), 7.86 (m, 2H, Aromatics), 7.48 (m, 8H, Aromatics), 6.99 (d, J=12.2 Hz, 1H, CH), 6.81 (s, 1H, H_4), 6.69 (d, J=12.2 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 189.0, 160.8, 146.3, 139.3, 137.8, 137.0, 135.2, 134.0, 129.3, 129.2, 129.2, 129.1, 129.0, 128.9, 127.6. MS (70 eV) *m/z* (%): 302 (M^+, 0.5), 215 (6), 139 (26), 105 (100), 77 (84). Anal. calcd for $C_{19}H_{14}N_2O_2$, C 75.48, H 4.67, N 9.27; found, C 75.52, H 4.71, N 9.33.

Acknowledgements

A. Coelho is indebted to Fondos FEDER for a doctoral fellowship. E. Sotelo thanks the University of Santiago de Compostela for his appointment as Post doctoral fellow.

References

1. For the previous paper in this series, see: Sotelo, E.; Coelho, A.; Raviña, E. *Chem. Pharm. Bull.* **2003**, in press.
2. (a) Bristol, J. A.; Sircar, I.; Moss, W. H.; Evans, D. B.; Weishaan, E. *J. Med. Chem.* **1984**, *27*, 1099. (b) Sircar, I.; Duell, B. L.; Cain, M. H.; Burke, S. E.; Bristol, J. A. *J. Med. Chem.* **1986**, *29*, 2142. (c) Frank, H.; Heinisch, G. In *Pharmacologically Active Pyridazines. Part 2. Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier: Amsterdam, 1992; Vol. 29, p 141.
3. (a) Sauter, F.; Stanetty, P.; Blaschke, A.; Hermann, V. *J. Chem. Res. (S)* **1981**, 103. (b) Sauter, F.; Stanetty, P.; Blaschke, A.; Hermann, V. *J. Chem. Res. (M)* **1981**, 1087.
4. (a) Murineddu, G.; Cignarella, G.; Chelucci, G.; Loriga, G.; Pinna, G. A. *Chem. Pharm. Bull.* **2002**, *6*, 754. (b) Barlocco, D.; Cignarella, G.; Dal Piaz, V.; Giovannoni, M. P.; De Benedetti, P. G.; Fanelli, F.; Montesano, F.; Poggesi, E.; Leonardi, A. *J. Med. Chem.* **2001**, *15*, 2403. (c) Malinka, W. *Pharmazie* **2001**, *6*, 384. (d) Costantino, L.; Rastelli, G.; Gamberini, M. C.; Giovannoni, M. P.; Dal Piaz, V.; Vianello, P.; Barlocco, D. *J. Med. Chem.* **1999**, *11*, 1894.
5. (a) Parrot, I.; Ritter, I.; Wermuth, C. G. *Synlett* **2002**, *7*, 1123. (b) Parrot, I.; Rival, I.; Wermuth, C. G. *Synthesis* **1999**, 1163. (c) Aldous, D. J.; Bower, S.; Mooncroft, N.; Todd, M. *Synlett* **2001**, 150. (d) Draper, T. L.; Bailey, T. R. *J. Org. Chem.* **1995**, *60*, 748.
6. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Elsevier: Amsterdam, 2000; Vol. 3.
7. Coelho, A.; Sotelo, E.; Estévez, I.; Raviña, E. *Synthesis* **2001**, *6*, 871.
8. (a) Sotelo, E.; Coelho, A.; Raviña, E. *Tetrahedron Lett.* **2001**, *42*, 8633. (b) Coelho, A.; Raviña, E.; Sotelo, E. *Synlett* **2002**, *12*, 2062.
9. (a) Laguna, R.; Rodriguez-Liñares, B.; Cano, E.; Estévez, I.; Raviña, E.; Sotelo, E. *Chem. Pharm. Bull.* **1997**, *45*, 1151. (b) Sotelo, E.; Fraiz, N.; Yañez, M.; Laguna, R.; Cano, E.; Raviña, E. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 1575. (c) Sotelo, E.; Fraiz, N.; Yañez, M.; Laguna, R.; Cano, E.; Raviña, E. *Bioorg. Med. Chem.* **2002**, *10*, 2873.
10. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron* **1975**, *50*, 4467. (b) Campbell, I. B. In *Organocopper Reagents, A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University: Oxford, 1994; p 217 Chapter 10. (c) Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, p 521.
11. (a) Haider, N.; Käferböck, J. *Heterocycles* **2000**, *53*, 2527. (b) Toussaint, D.; Suffert, J.; Wermuth, C. G. *Heterocycles* **1994**, *38*, 1273. (c) Goodman, A. J.; Stanforth, S. P.; Tarbit, B.

Tetrahedron **1999**, *55*, 15067. (d) Draper, T. L.; Bailey, T. R. *J. Org. Chem.* **1995**, *60*, 748.
12. Estévez, I.; Coelho, A.; Raviña, E. *Synthesis* **1999**, 1666.
13. R'kyek, O.; Maes, B. U. W.; Jonkers, T. H. M.; Lemiére, G. L. F.; Dommisse, R. A. *Tetrahedron* **2001**, *57*, 10009.
14. Sotelo, E.; Raviña, E.; Estévez, I. *J. Heterocycl. Chem.* **1999**, *36*, 985.
15. Kundu, N. G.; Das, P. *J. Chem. Soc., Chem. Commun.* **1995**, 99.
16. Das, P.; Kundu, N. G. *J. Chem. Res. (S)* **1996**, 298.
17. Kundu, N. G.; Das, P.; Balzarini, J.; De Clercq, E. *Bioorg. Med. Chem.* **1997**, *5*, 2011.
18. Minn, K. *Synlett* **1991**, 115.
19. Müller, Th.; Ansorge, M.; Aktah, D. *Angew. Chem. Int. Ed.* **2000**, *39*, 1253.
20. Müller, Th.; Braun, R.; Ansorge, M. *Org. Lett.* **2000**, *2*, 1967.
21. Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **1995**, *117*, 9786.
22. Saïah, M. K. E.; Pellicciari, R. *Tetrahedron Lett.* **1995**, *36*, 4497.
23. Ma, D.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1989**, 890.