Pyridazine Derivatives 32[1]: Stille-Based Approaches in the Synthesis of 5-Substituted-6-phenyl-3(2*H*)-pyridazinones

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Received October 29, 2002; accepted January 19, 2003

A series of 6-phenyl-3(2*H*)-pyridazinones bearing different substituents in the 5-position of the pyridazinone ring were prepared using Stille-based approaches in the search for new platelet-aggregation inhibitors.

Key words pyridazinone; palladium

Thrombosis is the pathological extension of the normal haemostatic process that is required to prevent blood loss following damage to the vascular wall. Uncontrolled platelet aggregation and platelet adhesion to the subendotelium of damaged blood vessels causes life-threatening diseases such as myocardial infarction, transient ischemic attack and unstable angina.[2)]

In recent years, the 6-aryl-3(2*H*)-pyridazinones have demonstrated a range of pharmacological activities,[3)] most of which are related to the cardiovascular system and especially to their properties as ionotropic or platelet aggregation inhibitors.[4—7)] Among these compounds, Imazodan (Ia), CI-930 (Ib), Indolindan (II), Bemoradan (III), Pimobendan (IV) and Zardaverine (V) (Fig. 1) are a few examples of pyridazinones that are active as cardiotonic agents.

For several years we have been involved in a medicinal chemistry programme to study the pharmacological exploitation of the 6-aryl-3(2*H*)-pyridazinone system. Many of the pyridazines and 6-aryl-3(2*H*)-pyridazinones obtained in our laboratory during this period show antihypertensive action[8—10)] or platelet inhibitory activity.[11—13)] Of particular interest are our systematic studies on 5-substituted-3(2*H*)-pyridazinones, which have led to the development of new potent platelet antiaggregation agents.[14,15)] These results motivated us to develop new and efficient synthetic strategies to allow the preparation of pyridazinones bearing different functional groups at position 5 of the heterocyclic ring.[16)] We have therefore decided to focus on the direct preparation of these compounds by palladium-catalysed carbon–carbon bond formation[17—20)] from readily obtainable, inexpensive 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1**.[21)] The palladium cross-coupling procedures offer the potential of a simple and adaptable method to introduce a wide range of residues at position 5 of halopyridazinones, which in turn allows a rapid pharmacomodulation of this series.[22,23)]

As part of a programme aimed at developing simple and efficient syntheses of pharmacologically useful pyridazinones we report here the application of a practical Stille cross-coupling reaction[24,25)] to synthesize a variety of novel and diversely functionalized 5-oxygenated-6-phenyl-3(2*H*)-pyridazinones.

The general synthetic strategy followed for the preparation of the 5-substituted pyridazinones is outlined in Charts 1—3. The starting material chosen for these transformations was the inexpensive 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1**.[21)] Compound **1**, like other haloderivatives in the 3(2*H*)-pyridazinone series, is almost unreactive under palladium cross-coupling reactions and the NH group in **1** was therefore protected as the methoxymethyl derivative **2** (85%). Once the precursor had been suitably protected the functionalization of **2** could be studied using the classical Stille reaction conditions.

Optimisation of the experimental conditions revealed that reaction of **2** with tributyl(vinyl)tin proceeded almost instantly using dry toluene as the solvent and bis(triphenylphosphine)palladium(II) dichloride as a palladium source to afford the 5-vinylderivative **3** in almost quantitative yield (Chart 1). Ozonolysis of the vinyl group in **3** and subsequent treatment with dimethylsulfide gave the methoxymethyl derivative **4**, which is a useful intermediate for further elaboration, and hydrolysis with hydrochloric acid gave aldehyde **5**. Compound **5** has previously been obtained by our group using a long-winded multistep route[14)] and so this new Stille-based synthetic strategy is a much-improved, highly efficient

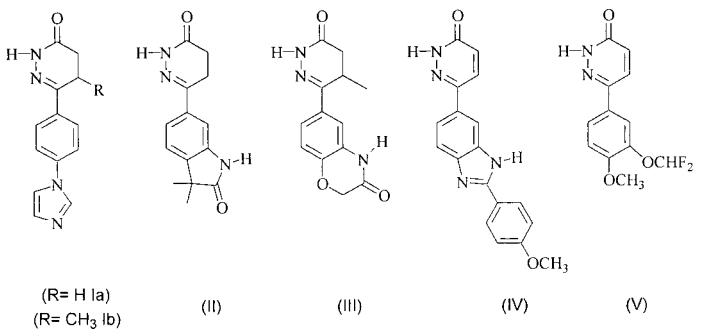

Fig. 1. Examples of Pharmacologically Useful 3(2*H*)-Pyridazinones

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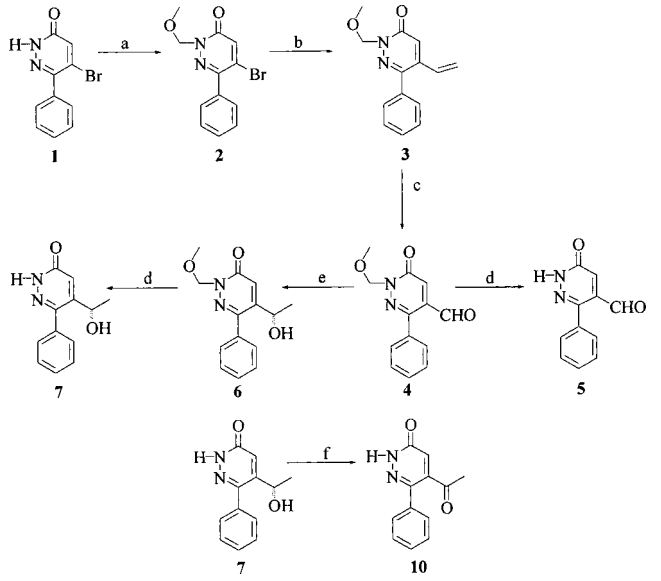


a: $ClCH_2OCH_3$, *N*,*N*-diisopropylethylamine, 4-DMAP, CH_2Cl_2, 0 °C; b: tributyl(vinyl)tin, $PdCl_2(PPh_3)_2$, toluene, 90 °C; c: O_3, SMe_2, CH_2Cl_2, −78 °C; d: 6 N HCl, reflux; e: MeLi, THF, −78 °C; f: MnO_2/THF.

Chart 1

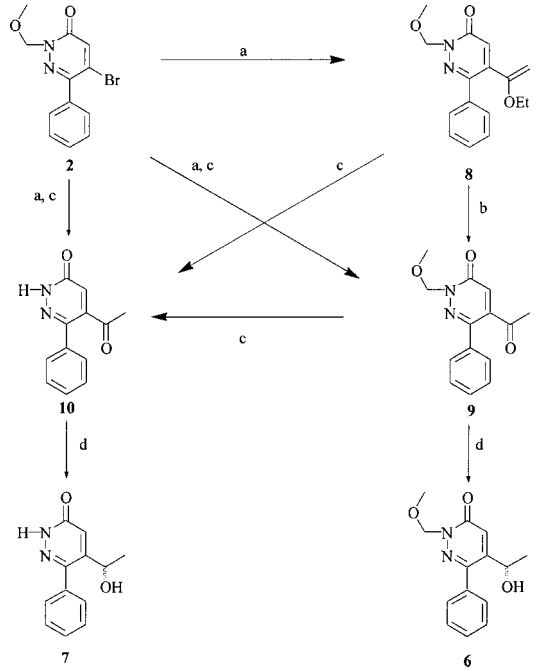
and mild procedure to obtain **5**.

Unfortunately, all attempts to obtain compound **7** by direct addition of methyllithium to the aldehyde **5** were unsuccessful (Chart 1). It was therefore decided to replace aldehyde **5** with the methoxymethyl derivative **4**, which does react with methyllithium to afford alcohol **6** (65%). Removal of the protecting group was accomplished by treatment of **6** with hydrochloric acid to give the desired alcohol **7** in moderate yield (65%). Manganese dioxide oxidation of **7** allow to prepare the methyl ketone **10** in 86%.

In order to shorten the synthetic steps to prepare ketone **10** and to obtain novel 5-substituted-pyridazinones, we developed another efficient and highly versatile Stille-based synthetic alternative to prepare pyridazinones containing oxygenated functions at position 5 of the heterocyclic ring (Chart 2). Starting from 5-bromo-2-methoxymethyl-6-phenyl-3-pyridazinone **2**, the palladium-catalysed reaction with tributyl(1-ethoxyvinyl)tin afforded, in high yield and depending on the final reaction conditions, the isolable 5-ethoxyvinyl-2-methoxymethyl-6-phenyl-3-pyridazinone **8**, the methylketone **10** or the protected methylketone **9**. Reduction of the carbonyl group in ketones **9** and **10** by treatment with sodium borohydride in methanol allow to obtain the alcohols **6**, **7**. Curiously, during these proceses we have also isolated variable ammounts of by products as consequence of the reduction of the double bond at positions 4- and 5- of the heterocycle.

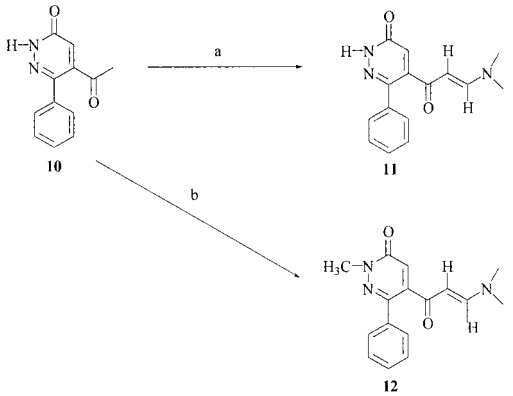
Condensation of ketone **10** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) gave enamine **11**. On using a large excess of DMFDMA in this reaction we obtained the methyl derivative **12** in excellent yield (90%) (Chart 3). Analysis of the NMR data for compounds **11** and **12** reveals a *trans* stereochemistry of the double bonds (J=15—16 Hz).

In summary, we have developed two practical and efficient Stille-Based procedures which permit to access, in a shorten synthetic sequence, to different 6-phenyl-5-substituted-3(2*H*)-pyridazinones. The biological activity of the obtained



a: Tributyl(1-ethoxyvinyl)tin, $PdCl_2(PPh_3)_2$, toluene, 90 °C, 2 h; b: 5% HCl, r.t.; c: 6 N HCl reflux; d: $NaBH_4$, MeOH

Chart 2



a: DMFDMA, benzene, reflux; b: DMFDMA, reflux

Chart 3

compounds is under study and will be published in due time.

Experimental

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 1640 FTIR spectrophotometer. ^{1}H-NMR spectra were obtained on Bruker WM250 and AM300 Hz spectrometers using tetramethylsilane as internal standard (chemical shifts are in δ values, J in Hz). Mass spectra were recorded on a Varian MAT-711 instrument. Elemental analyses were performed on a Perkin-Elmer 240B apparatus at the Microanalysis Service of the University of Santiago de Compostela. The progress of the reactions was monitored by thin layer chromatography with 2.5 mm Merck silica gel GF 254 plates, and the purified compounds each showed a single spot; unless otherwise stated iodine vapour and/or UV light were used for detection. Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 40, 0.040—0.063 mm).

5-Bromo-6-phenyl-3(2*H*)-pyridazinone (1) This compound was prepared following our previously described procedure.[21)]

5-Bromo-2-methoxymethyl-6-phenyl-3-pyridazinone (2) Methoxymethyl chloride (1.28 ml, 16.9 mmol) was added to a suspension of 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1** (1.7 g, 6.77 mmol), 4-dimethyl-

aminopyridine (5 mg) and *N*,*N*-diisopropylethylamine (1.76 ml, 10.1 mmol) in anhydrous methylene chloride (12 ml) at 0 °C. The mixture was stirred for 1 h at 0 °C. The reaction was allowed to warm up to room temperature and stirred for a further 2 h. The solvent was evaporated to give a yellow oil, which was purified by column chromatography (silica gel, ethyl acetate/hexane 1 : 3) to afford colourless needles (1.71 g, 85%). mp 103 °C. IR (KBr): 1669 (C=O), 1053 (C–O–C) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ: 3.42 (s, 3H, OCH_3), 5.45 (s, 2H, CH_2O), 7.21 (s, 1H, H_4), 7.40 (m, 3H, aromatics), 7.63 (m, 2H, aromatics). *Anal.* Calcd for $C_{12}H_{11}BrN_2O_2$: C, 48.84; H, 3.76; Br, 27.07; N, 9.49. Found: C, 48.97; H, 3.82; N, 9.53.

2-Methoxymethyl-6-phenyl-5-vinyl-3-pyridazinone (3) A mixture of 5-bromo-2-methoxymethyl-6-phenyl-3-pyridazinone **2** (3.38 mmol), bis-(triphenylphosphine)palladium(II) dichloride (1.18 mg, 0.167 mmol) and tributyl(vinyl)tin (1.089 ml, 3.72 mmol) in anhydrous toluene (16 ml) was heated under reflux under argon for 2 h. During the course of the reaction the colour changed from yellow to black and this was accompanied by the formation of a precipitate. 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. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1 : 1) to afford **3** as a yellow oil, which crystallized on standing; yield: 0.75 g (95%), oil. IR (KBr): 1669 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ: 3.48 (s, 3H, OCH_3), 5.47 (s, 2H, CH_2O), 5.50 (d, J=11.0 Hz, 1H, HC=CH_2), 5.83 (d, J=17.7 Hz, 1H, HC=CH_2), 6.41 (dd, J=11.0, 17.7 Hz, 1H, HC=CH_2), 7.04 (s, 1H, H_4), 7.42 (s, 5H, aromatics). *Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.54; H, 5.88; N, 11.61.

2-Methoxymethyl-5-formyl-6-phenyl-3(2*H*)-pyridazinone (4) To a solution of compound **3** (1 g, 4 mmol) in anhydrous methylene chloride (30 ml) at −78 °C was passed a slow flow of ozone for 10 min. After this time, methyl sulfide (2 ml) was added and the mixture was stirred overnight under a nitrogen atmosphere. Evaporation of the solvent under reduced pressure gave a crude solid, which was purified by column chromatography (silica gel, ethyl acetate/hexane 1 : 1) to give aldehyde **4** (0.63 g, 85%). mp 79.3—81.0 °C. IR (KBr): 2720 (CHO), 1710 (CHO), 1680 (CO), 1590 (aromatics). ^{1}H-NMR ($CDCl_3$): δ: 3.38 (s, 3H, CH_3), 5.39 (s, 2H, –CH_2), 7.38 (s, 1H, H_4), 7.55—7.47 (m, 5H, aromatics), 9.82 (s, 1H, CHO). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.35; H, 4.99; N, 11.58.

5-Formyl-6-phenyl-3(2*H*)-pyridazinone (5) A solution of the methoxymethyl derivative **4** (0.20 g, 1.0 mmol) in MeOH (10 ml) was treated with 6 N HCl (7 ml) and the mixture was heated under reflux (90 °C) for 24 h. The mixture was poured onto ice and the resulting solid was recrystallized from 2-propanol to give a white solid (0.15 g, 95%). mp 230.0—231.2 °C. IR (KBr): 3180—3050 (NH), 2720 (CHO), 1720 (CHO), 1650 (CO), 1590 (aromatics). ^{1}H-NMR ($CDCl_3$): δ: 7.46 (s, 1H, H_4), 7.70—7.60 (m, 5H, aromatics), 9.87 (s, 1H, CHO), 13.82 (s, 1H, NH). *Anal.* Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.97; H, 4.06; N, 14.34.

5-(1′-Hydroxyethyl)-2-methoxymethyl-6-phenyl-3(2*H*)-pyridazinone (6) To a solution of ketone **9** (120 mg, 0.46 mmol) in MeOH (25 ml) was added slowly sodium borohydride (26 mg, 0.69 mmol) and the suspension was stirred at room temperature during 30 min. The reaction mixture was treated with water (25 ml) and the solution extracted with methylene chloride, dried (Na_2SO_4), and the solvent removed to give a colourless oil, which was purified by column chromatography (silica gel, ethyl acetate/hexane 1 : 2) to give the product as a colourless oil (78 mg, 65%). IR (KBr): 3235 (OH), 1680 (CO), 1580 (aromatics), 1150 (C–O–C). ^{1}H-NMR ($CDCl_3$): δ: 1.03 (d, 3H, CH_3), 3.41 (s, 3H, OCH_3), 4.66 (br s, 1H, OH), 5.38 (s, 2H, N–CH_2–O), 5.54 (q, 1H, CH), 7.10 (s, 1H, H_4), 7.53 (s, 5H, aromatics). *Anal.* Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.70. Found: C, 64.79; H, 6.27; N, 110.59.

5-(1′-Hydroxyethyl)-6-phenyl-3(2*H*)-pyridazinone (7) To a solution of ketone **10** (250 mg, 1.16 mmol) in MeOH (25 ml) was added slowly sodium borohydride (26 mg, 1.75 mmol) and the mixture was stirred at room temperature during 30 min. The reaction mixture was treated with water (25 ml) and the product extracted with methylene chloride. The organic layers were dried (Na_2SO_4) and the solvent was removed to give an oil, which was purified by column chromatography (silica gel, ethyl acetate/hexane 2 : 1) to afford the product as a colourless oil (163 mg, 65%). IR (KBr): 3255 (OH), 1680 (CO), 1590 (aromatics). ^{1}H-NMR ($CDCl_3$): δ: 1.01 (d, 3H, CH_3), 4.58 (br s, 1H, OH), 5.43 (q, 1H, CH), 6.95 (s, 1H, H_4), 7.45 (m, 5H, aromatics), 13.00 (s, 1H, NH). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.73; H, 5.71; N, 13.08.

2-Methoxymethyl-6-phenyl-5-[(1′-ethoxy)vinyl]-3-pyridazinone (8) A mixture of 5-bromo-2-methoxymethyl-6-phenyl-3-pyridazinone **2** (1.5 g, 5.08 mmol), bis(triphenylphosphine)palladium(II) dichloride (2.01 mg, 0.25 mmol) and tributyl(1-ethoxyvinyl)tin (1.887 ml, 5.58 mmol) in anhydrous toluene (16 ml) was heated under reflux under argon for 2 h. During the course of the reaction the colour changed from yellow to black and this was accompanied by the formation of a precipitate. 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 residue, which was purified by column chromatography (silica gel, ethyl acetate/hexane 2 : 1) to afford compound **8** as a brown oil (1.42 g, 98%). IR (KBr): 1674 (C=O), 1053 (C–O–C) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ: 0.81 (t, J=6.9 Hz, 3H, CH_3), 3.49 (s, 3H, CH_3O) 4.31 (q, J=6.9 Hz, 1H), 4.43 (d, J=2.1 Hz, 1H), 5.48 (s, 2H, CH_2O), 7.01 (s, 1H, H_4), 7.37 (m, 5H, aromatics). *Anal.* Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.97; H, 4.06; N, 14.34.

5-Acetyl-2-methoxymethyl-6-phenyl-3(2*H*)-pyridazinone (9) This compound was synthesised by treatment of **8** with 5% hydrochloric acid at room temperature in toluene for 12 h. The product was extracted with methylene chloride (3×15 ml), dried (Na_2SO_4) and the solvent evaporated. The resulting yellow oil was purified by column chromatography (silica gel, ethyl acetate/hexane 3 : 2) to give a colourless oil (157 mg, 90%). IR (KBr): 1718 ($COCH_3$), 1676 (CO), 1099 (C–O–C). ^{1}H-NMR ($CDCl_3$): δ: 2.15 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 5.50 (s, 2H, CH_2), 7.43 (s, 1H, H_4), 7.44 (m, 5H, aromatics). *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.24; H, 5.47; N, 10.89. This compound can be obtained in a one-pot procedure by treating compound **6** with tributyl(1-ethoxyviny)tin, as described in the general procedure, followed by treatment with 5% HCl at room temperature for 12 h.

5-Acetyl-6-phenyl-3(2*H*)-pyridazinone (10) This compound was synthesised by treatment of **8** with 6 N hydrochloric acid. The mixture was heated under reflux for 12 h and the product then extracted with methylene chloride (3×15 ml), dried (Na_2SO_4) and the solvent evaporated. The resulting colourless oil was purified by column chromatography (silica gel, ethyl acetate/hexane 1 : 1) to afford a white solid (710 mg, 90%), which was recrystallized from 2-propanol. mp 188.2 °C. A one-pot preparation was also undertaken (following the Stille coupling general procedure for compound **6**), followed by treatment with 6 N HCl–a process that directly gives compound **10**. IR (KBr): 3100—2900 (NH), 1702 ($COCH_3$), 1674 (CO). ^{1}H-NMR ($CDCl_3$): δ: 2.14 (s, 3H, CH_3), 7.43 (s, 1H, H_4), 7.44 (m, 5H, aromatics), 12.64 (bs, 1H, NH). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.37; H, 4.71; N, 13.12.

5-(3′-Dimethylamino-2′-en-propionyl)-6-phenyl-3(2*H*)-pyridazinone (11) A mixture of compound **10** (31 mg, 0.14 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.036 ml, 0.27 mmol) in benzene (5 ml) was heated under reflux during 6 h. The reaction mixture was evaporated to dryness and the residue washed with water. The product was extracted into methylen chloride, dried ($NaSO_4$) and purified by column chromatography (silica gel, chloroform/methanol 13 : 0.5) to afford a yellow oil (35 mg, 90%). IR (KBr): 2925 (NH), 1669 (CO), 1712 (CO). ^{1}H-NMR ($CDCl_3$): δ: 2.78 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 5.07 (d, J=9.5 Hz, 1H, HC=C), 6.98 (d, J=9.5 Hz, 1H, C=CH), 7.26 (s, 1H, H_4), 7.38 (m, 3H, aromatics), 7.53 (m, 2H, aromatics), 11.30 (bs, 1H, –NH). *Anal.* Calcd for $C_{15}H_{15}N_3O_2$: C, 66.99; H, 5.61; N, 15.60. Found: C, 66.92; H, 5.63; N, 15.64.

5-(3′-Dimethylamino-2′-propienyl)-2-methyl-6-phenyl-3(2*H*)-pyridazinone (12) A suspension of compound **10** (31 mg, 0.14 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (2 ml, 15 mmol) was heated under reflux during 6 h. The reaction mixture was evaporated to dryness and the residue washed with water, extracted into methylene chloride, dried ($NaSO_4$) and purified by column chromatography (silica gel, chloroform/methanol 13 : 0.5) to afford a yellow oil (37 mg, 90%). IR (KBr): 1697 (CO), 1651 (CO), 1570 (aromatics),. ^{1}H-NMR ($CDCl_3$): δ: 2.76 (s, 3H, –CH_3), 3.09 (s, 3H, CH_3), 3.86 (s, 3H, N–CH_3), 5.07 (d, J=11.6 Hz, 1H, HC=C), 6.96 (d, J=11.6 Hz, 1H, C=CH), 7.36 (s, 1H, H_4), 7.51 (m, 3H, aromatics), 7.52 (m, 2H, aromatics). *Anal.* Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.85; H, 6.05; N, 14.84.

Acknowledgements Financial support from the Xunta de Galicia (Project XUGA 8151389) is gratefully acknowledged. We also thank the Spanish Instituto de Cooperación Iberoamericana (ICI) for a Doctoral fellowship for Eddy Sotelo.

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