Pyridazines Part XXIII:[1] Efficient Arylation at Position 5 of the 6-Phenyl-(2*H*)-pyridazin-3-one System Using a Suzuki Cross-Coupling Reaction

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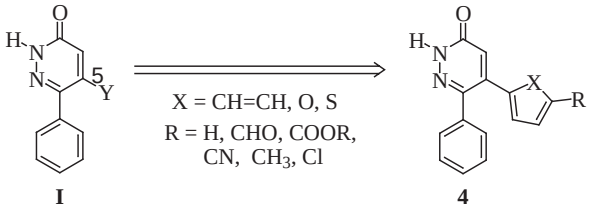
Dedicated to the Memory of Professor Raymond N. Castle

Abstract: A highly efficient procedure for introducing aryl or heteroaryl rings at position 5 of the 6-phenyl-(2*H*)-pyridazin-3-one system using a Suzuki cross-coupling reaction has been developed in the search for new platelet aggregation inhibitors.

Key words: arylations, palladium, catalysis, pyridazin-3-ones

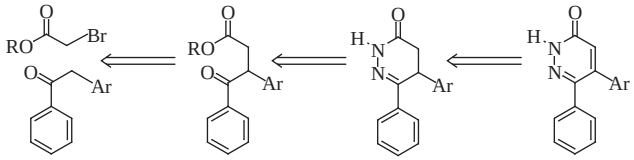
The pyridazine system, which has been known for almost a century and may be considered as a bioisoster of benzene or of other heterocycles, aroused little interest in medicinal chemistry until its discovery in medicinally useful natural compounds. Today the pyridazine nucleus and its 3-oxo derivatives [(2*H*)-pyridazin-3-ones] are recognised as versatile pharmacophores with a variety of biological activities[2] and can be used to support other pharmacophoric groups. Among the pyridazines developed in the past 15 years as drug candidates or pharmacological tools, 6-aryl-(2*H*)-pyridazin-3-ones and their 4,5-dihydro derivatives have attracted particular attention due to their important cardiovascular effects.[3] For example, many of the pyridazines and 6-aryl-(2*H*)-pyridazin-3-ones obtained in our laboratory during this period are endowed with antihypertensive action[4] or are powerful inhibitors of platelet aggregation.[5–8] Particularly, our studies on 5-amino[6] and 5-oxygenated[7] pyridazinones have led to the development of new platelet antiaggregation agents with a non c-AMP PDE III-based mechanism.[8,9] These results have motivated us to prepare other 5-substituted-(2*H*)-pyridazin-3-ones, having alkenyl groups at 5-position, which are potent antiplatelet agents.[10] In continuance of this work, we have now designed a series of 5-aryl-6-phenyl-(2*H*)-pyridazin-3-ones **4**, that can be considered as vinylogues of the precursor pyridazinone **I**. The effects of the aryl ring at position 5 are expected to induce steric perturbations and would permit the modulation of the antiplatelet activity, affording compounds that would possess an enhanced platelet inhibitory effect (Figure 1).



I **4**

Figure 1

Most syntheses of 5-substituted-(2*H*)-pyridazin-3-ones proceed via traditional methods,[11] involving condensation of hydrazine with appropriate substituted lactones or 1,4-dicarbonyl compounds (Figure 2). Concretely, these synthetic routes to obtain 6-phenyl-(2*H*)-pyridazin-3-ones with aryl or heteroaryl substituents at position 5 are unattractive because the required starting arylmethylphenylketones **II** or heteroarylketoesters **III** are not commercially available.



II **III** **IV** **4**

Figure 2

We have therefore focused on the direct preparation of compounds **4** from readily obtainable, inexpensive 5-bromo-6-phenyl-(2*H*)-pyridazin-3-one (**1**) by palladium-catalysed carbon-carbon bond formation. The Suzuki cross-coupling-based[12] procedure to obtain compounds **4** offers the potential of a more adaptable and simple method to introduce a wide range of aryl residues at position 5 of halopyridazinones, which permit a rapid pharmacomodulation of this series.

Cross-coupling reactions catalysed by transition metals represent a powerful method for the formation of carbon-carbon bonds[13] and have been especially popular due to their application in the preparation of complex natural products, heterocycles and in supramolecular chemistry.[13,14] Curiously, very little appears to have been published on palladium-catalysed reactions of pyridazines.[15] Although we recently reported the synthesis of several 5-vinyl- and 5-alkynyl-6-phenyl-(2*H*)-pyridazin-3-ones by the Stille, Heck or Sonogashira approaches,[16] no successful arylation of the pyridazinone system using Suzuki cross-coupling methodology has hitherto been described. Neutral 3- and 6-halopyridazines have been coupled with arylboronic acids[17] but the difference in acidity between

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these substrates and pyridazinones[11] leads one to expect significantly different coupling behaviour.

As part of a program aimed to develop simple and more efficient syntheses of pharmacologically useful pyridazinones, we herein report the application of simple and practical Suzuki cross-coupling reactions to synthesise a variety of novel 5-aryl or 5-heteroaryl-6-phenyl-(2*H*)-pyridazin-3-ones 4a-f.

In a preliminary experiment we have used 5-bromo-6-phenyl-(2*H*)-pyridazin-3-one (**1**)[6] as starting material. Disappointingly all attempts to perform the cross-coupling reaction between **1** and arylboronic acids under classical Suzuki conditions [sodium or potassium carbonate as base, tetrakis(triphenylphosphine)palladium as catalyst and a mixture of toluene/ethanol as solvent] afforded only 10% of the coupling products. More than 85% of precursor **1** was recovered. Furthermore, experiments with benzeneboronic acid, varying the solvent (DMF, THF or 1,2-methoxyethane) and/or base (triethylamine, sodium bicarbonate, potassium carbonate, sodium or potassium hydroxide), and the 6-phenyl-5-iodo-(2*H*)-pyridazin-3-one failed to improve the results.

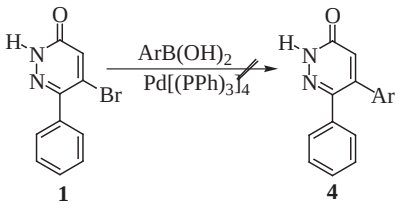


Figure 3

The above failures are not attributable to the approach of the palladium catalyst to the C-Br bond of the substrate, being impeded by the bulky phenyl ring at position 6. Our recent structural studies in this series, employing molecular modelling techniques[10] and X-ray crystallographic analyses,[18] have shown that for the 5-substituted 6-phenyl-(2*H*)-pyridazin-3-ones the phenyl group at C-6 is essentially orthogonal to the heterocyclic ring and should therefore not hinder cross-coupling.

As part of these studies we have evaluated the effect of several bases on the phenylation of **1** using a 2:1 mixture of toluene/ethanol as solvent (Table 1). Although none of these experiments permits to obtain compound **4** in high yield, we have observed an important effect of the base on the coupling reaction. Thus, strong bases (sodium or potassium hydroxide) completely suppressed the reaction. The low reactivity experienced and the negative effect of strong bases on the coupling reaction are attributable to the acidity of the NH group or rather to the lactam function [(2*H*)-Pyridazin-3-one is about as acidic as phenol with a PK_a of 10.5].

It is well established that an important requirement for the Suzuki coupling is the halide being electron-deficient.[19] Under the basic conditions required for the Suzuki arylation, the 5-bromopyridazin-3-one **1** becomes negatively

able 1 Effect of the Base on the Cross-Coupling Reaction between **1** and Benzeneboronic Acid in Toluene–Ethanol and using Tetakis(triphenylphosphine)palladium as Catalyst

ase	Yield (%)[a]
$aHCO_3$	8
a_2CO_3	10
aOH	–
OH	–

Determined by GC

charged due to the formation of a salt, which decreases the reactivity of the halide. Hence, Pd-insertion into the C-Br bond becomes more difficult. In order to confirm this hypothesis, we proceeded to subject 5-bromo-2-methyl-6-phenylpyridazin-3-one and phenylboronic acid to the above-described coupling conditions. Satisfyingly, they afforded the desired 5-phenylated product **6** in nearly quantitative yield (95%), showing that the low reactivity of this system is due to the acidity of the NH group at position 2.

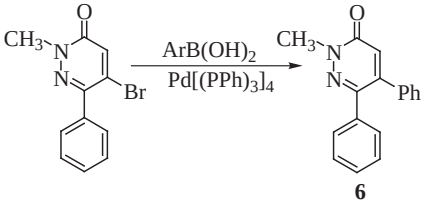


Figure 4

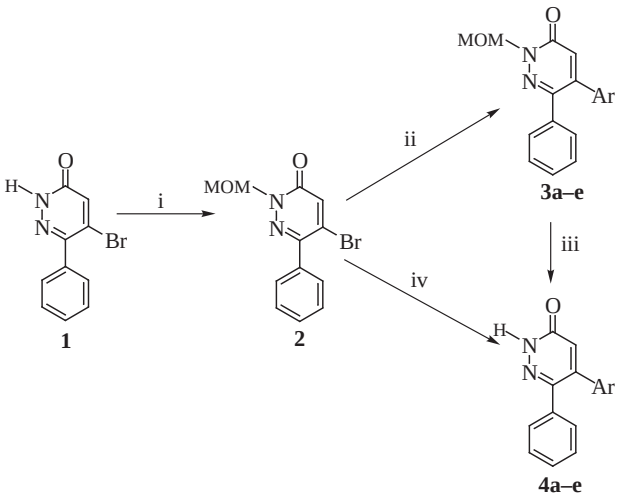
In subsequent work, we protected the NH group of **1** with the methoxymethyl (MOM) group which can be removed more easily than the methyl group of **6** by treatment of the 2-methoxymethylpyridazinones with hydrochloric acid.[10,16] After some optimisation, we found that the reaction of the MOM-protected substrate **2** with arylboronic acids

able 2 5-Aryl-6-phenyl-(2*H*)-pyridazin-3-ones **4a–f** and Their 2-ethoxymethyl Precursors **3a–f** Prepared from **2**

ompound	Ar	Yield (%)	Compound	Yield[a] (%)
a	Phenyl	98	**4a**	93
b	4-Cl-phenyl	89	**4b**	85
c	4-CH_3-phenyl	96	**4c**	90
d	4-CHO-phenyl	92	**4d**	90
e	2-Furyl	94	**4e**	88
f	2-Thienyl	18/70[b]	**4f**	10/65[b]

Yields of the one-pot procedure.
Yield using DME as solvent.

took place in nearly quantitative yields (Table 2), using 2:1 toluene-ethanol as solvent, potassium carbonate as base and tetrakis(triphenylphosphine)palladium as palladium source (Scheme 1).



Scheme 1 Reagents and conditions: (i) ClMOM-CH_2Cl_2, DMAP, (*i*-Pr)$_2$NEt, 0 ºC, 12 h; (ii) ArB(OH)$_2$, Pd(PPh$_3$)$_4$, K_2CO_3, EtOH–toluene, reflux, 2–6 h; (iii) 6 N HCl, reflux, 6 h; (iv) a) ArB(OH)$_2$, Pd(PPh$_3$)$_4$, K_2CO_3, EtOH–toluene, reflux, 2–6 h; b) 6 N HCl, reflux, 8 h

Unexpectedly, the reaction of **2** with 2-thienylboronic acid under the above conditions gave only a poor yield (10%) of the required 2-methoxymethyl-6-phenyl-5-(2-thienyl)pyridazin-3-one (**3f**) and most of the substrate **2** was simply debrominated to give the 2-methoxymethyl-6-phenylpyridazin-3-one (70%). However, a 70% yield of **3f** was obtained when, following Gronowitz´s recommendations concerning troublesome couplings,[20] we carried out the reaction in 1,2-dimethoxyethane (DME).

The MOM protecting group was easily cleaved from the 5-aryl-2-methoxymethyl-6-phenylpyridazin-3-ones **3a-f** by treatment with refluxing 6 N HCl for 6 h, which afforded the pyridazinones **4a-f** in 65–93 % yields.

Furthermore, we found that the sequence **2** Æ **3** Æ **4** could be carried out in a one-pot reaction, monitoring the progress of the cross-coupling reaction by TLC and adding 6 N HCl when the reaction was complete (Scheme 1). The broader potential of this new synthetic route is illustrated not only by using different arylboronic acids, but also by the successful preparation of compounds **5a-c**, which were required for our structure-activity relationship studies (Scheme 2).

In conclusion, we have applied the Suzuki cross-coupling methodology to develop a general, rapid, and practical one-pot synthesis of 5-aryl-6-phenyl-(2*H*)-pyridazin-3-ones **4** starting from the 2-methoxymethyl derivative of readily available 5-bromo-6-phenyl-(2*H*)-pyridazin-3-one **1**. Further investigations are now in progress in order to obtain new 5-aroyl derivatives by carbonylation procedures. A full account of the antiplatelet activity and mechanism of action of this series will be published in due course.

Melting points were measured on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1640 FT-IR spectrophotometer. ^{1}H NMR spectra were obtained on Bruker WM250 and AM300 spectrometers using tetramethylsilane as in-

able 3 Spectroscopic Data of Pyridazin-3-ones **3a–f**

ompound	Mp (°C)	IR (KBr) (cm^{-1})	MS *m/z* (%)	^{1}H NMR (CDCl$_3$) δ, *J* (Hz)[b]
a	Oil	1562, 1590	292 (M$^+$, 27), 249 (100)	7.34–7.20 (m, 10H, Ph), 6.98 (s, 1H, H-4), 5.56 (s, 2H, N-CH_2), 3.44 (s, 3H, OCH_3)
b	136.0–136.5[a]	1656, 1592	326 (M$^+$, 8), 225 (100)	7.40–7.30 (m, 5H, Ph), 7.17 (d, *J* = 8.3, 2H, Ar), 7.04 (d, *J* = 8.03, 2H, Ar), 6.95 (s, 1H, H-4), 5.55 (s, 2H, CH_2), 3.55 (s, 3H, CH_3)
c	Oil	1667, 1588	262 (M$^+$, 100)	7.32–7.24 (m, 5H, Ph), 7.14 (d, *J* = 8.0, 2H, Ar), 6.98 (d, *J* = 8.0, 2H, Ar), 6.94 (s, 1H, H-4), 5.54 (s, 2H, CH_2), 3.55 (s, 3H, OCH_3), 2.15 (s, 3H, C-CH_3)
d	Oil	1710, 1664	320 (M$^+$, 12), 219 (100)	9.98 (s, 1H, CHO), 7.78 (d, *J* = 8.3, 2H, Ar), 7.30 (d, *J* = 8.3, 2H, Ar), 7.25–7.14 (m, 5H, Ph), 6.99 (s, 1H, H-4), 5.53 (s, 2H, CH_2), 3.55 (s, 3H, CH_3)
e	102.0–102.7[a]	1661, 1589	282 (M$^+$, 16), 181 (100)	7.51–7.37 (m, 6H, 5H Ph + 1H furan), 7.31 (s, 1H, H-4), 6.28 (dd, *J* = 3.5 and 1.8, 1H, furan), 5.66 (d, *J* = 3.5, 1H, furan), 5.49 (s, 2H, CH_2), 3.51 (s, 3H, CH_3)
f	Oil	1671, 1592	298 (M$^+$, 15), 197 (100)	7.33 (m, 6H, 5H Ph + 1H thiophene), 7.04 (s, 1H, H-4), 6.86 (dd, *J* = 3.9 and 4.7, 1H, thiophene), 6.71 (d, *J* = 2.9, 1H, thiophene), 5.47 (s, 2H, CH_2), 3.49 (s, 3H, CH_3)

Recrystallised from acetonitrile.
NMR data were recorded at 300 MHz.

able 4 Analytical and Spectroscopic Data of Pyridazin-3-ones **4a–f**

ompound	Mp (°C)[a]	IR (KBr) (cm^{-1})	MS *m/z* (%)	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)[b]	Analysis	Calcd/Found (%)
					C	H
a	178.5–180.6	1668 1589	248 (M^+, 100)	11.58 (br s, 1H, NH), 7.38–7.20 (m, 10H, Ph), 7.01 (s, 1H, H-4)	77.40/ 77.43	4.87/ 4.90
b	222.0–222.8	1664 1587	282 (M^+, 10), 247 (100)	11.65 (br s, 1H, NH), 7.40–7.30 (m, 5H, Ph), 7.16 (d, *J* = 8.4, 2H, Ar), 7.05 (d, *J* = 8.4, 2H, Ar), 6.97 (s, 1H, H-4)	67.97/ 67.98	3.92/ 3.95
c	198.0–200.0	1663 1584	262 (M^+, 100)	11.40 (br s, 1H, NH), 7.41–7.29 (m, 5H, Ph), 7.18 (d, *J* = 8.0, 2H, Ar), 7.06 (d, *J* = 8.0, 2H, Ar), 7.01 (s, 1H, H-4), 2.33 (s, 3H, CH_3)	77.84/ 77.88	5.38/ 5.38
d	172.3–173.0	1665 1588	276 (M^+, 100)	13.07 (br s, 1H, NH), 9.98 (s, 1H, CHO) 7.78 (d, *J* = 8.2, 2H, Ar), 7.29 (d, *J* = 8.2, 2H, Ar), 7.25–7.11 (m, 5H, Ph), 6.98 (s, 1H, H-4)	73.90/ 73.92	4.38/ 4.39
e	235.0–235.5	1662 1580	238 (M^+,100)	12.05 (br s, 1H, NH), 7.48–7.33 (m, 7H, 5H Ph +1H furan + H-4), 6.28 (dd, *J* = 3.5 and 1.8, 1H, furan), 5.64 (d, *J* = 3.5, 1H, furan)	70.58/ 70.62	4.23/ 4.25
f	201.0–202.1	1667 1588	256 (M^+, 15), 167 (100)	11.41 (br s, 1H, NH), 7.35 (m, 6H, 5H Ph + 1H, thiophene), 7.10 (s, 1H, H-4), 7.00 (dd, *J* = 1.2 and 3.7, 1H, thiophene), 6.81 (dd, *J* = 3.7 and 5.1, 1H, thiophene)	66.12/ 66.13	3.96/ 3.94

Recrystallised from acetonitrile.
NMR data were recorded at 300 MHz.

ternal standard (chemical shifts are d values, *J* in Hz). Mass spectra were determined 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 strips, and the purified compounds each showed a single spot. Unless otherwise stated, iodine vapor 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-2-methoxymethyl-6-phenylpyridazin-3-one (2)

A mixture of bromopyridazinone **1** (1.70 g, 6.77 mmol), 4-*N*,*N*-dimethylaminopyridine (0.10 g) and *i*-Pr_2NEt (1.20 g, 1.62 mL, 10.1 mmol) in anhyd CH_2Cl_2 (12 mL) was stirred at 0 °C (ice bath) for 30 min. Methoxymethyl chloride (1.35 g, 1.28 mL, 1.69 mmol) was added and the mixture was stirred for 1 h at 0 °C and then allowed to warm to r.t. while stirring was continued for 2 h. The reaction mixture turned purple. Evaporation of the solvent gave a yellow oil which was purified by column chromatography (eluent: EtOAc–hexane, 1:3) affording a white solid, which was recrystallised from EtOAc to give compound **2** (1.71 g, 85%) as colourless needles; mp 103.0 °C.

IR (KBr): ν = 1669 (CO), 1748 (*C*-*O*-C) 1588 (aromatics) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.63 (m, 2H, Ar), 7.40 (m, 3H, Ar), 7.21 (s, 1H, H-4), 5.45 (s, 2H, CH_2), 3.42 (s, 3H, CH_3).

MS *m/z* (%): 296 (5), 294 (5), 265 (25).

Coupling Reaction Affording Compounds 3; General Procedure

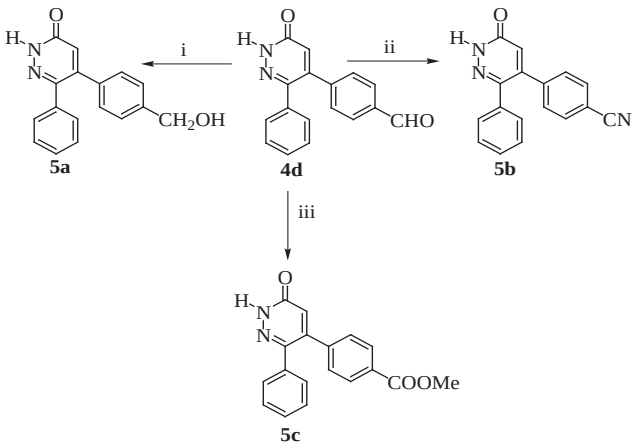
5-Bromo-2-methoxymethyl-6-phenylpyridazin-3-one (**2**) (0.47 g, 1.6 mmol) was mixed with arylboronic acid (2.2 mmol), $Pd(PPh_3)_4$ (0.018 g, 0.016 mmol) and K_2CO_3 (0.49 g, 5.08 mmol) in toluene-EtOH (2:1, 15 mL) (15 mL of DME for compound **3f**), flushed with argon for 5 min, and the mixture was then stirred and refluxed (oil bath, 120 °C) under argon until the starting material had disappeared (TLC monitoring). After cooling, the solution was concentrated to dryness under reduced pressure and the residue was purified by column chromatography on silica gel.

One-pot Procedure for the Coupling Reaction; General Procedure

5-Bromo-2-methoxymethyl-6-phenylpyridazin-3-one (**2**) (0.47 g, 1.6 mmol) was mixed with arylboronic acid (2.2 mmol), $Pd(PPh_3)_4$ (0.018 g, 0.016 mmol) and K_2CO_3 (0.49 g, 5.08 mmol) in toluene-EtOH (2:1, 15 mL) (15 mL of DME for compound **4f**) was flushed with argon for 5 min, and the mixture was then stirred and refluxed (oil bath, 120 °C) under argon until the starting material had disappeared (TLC monitoring). 6 N HCl (20 mL) was subsequently added and the reaction mixture was refluxed (oil bath, 120 °C) for 6 h, allowed to cool to r.t., and concentrated to dryness under reduced pressure. The residue was then purified by column chromatography on silica gel.

Cleavage of the MOM Group from Compounds 3a–f; General Procedure

A solution of the 2-methoxymethylpyridazin-3-one **3a–f** (5 mmol) in EtOH (20 mL) was treated with 6 N HCl (10 mL) and the resulting mixture was refluxed (oil bath, 120 °C) for 6 h. After cooling the solvent was removed, the residue was extracted with CH_2Cl_2 (3 × 25



Scheme 2 Reagents and conditions: (i) $NaBH_4$/MeOH; (ii) NH_2OH•HCl/TFA, reflux, 3 h; (iii) NaCN/MeOH/MnO_2

mL) and dried (Na_2SO_4). Then the solution was concentrated to obtain a solid, which was recrystallised from the appropriate solvent.

5-(4-Hydroxymethylphenyl)-6-phenyl-(2*H*)-pyridazin-3-one (5a)

$NaBH_4$ (0.026 g, 0.69 mmol) was slowly added to a solution of the aldehyde **4d** (0.12 g, 0.46 mmol) in MeOH (25 mL) and the suspension was then stirred at r.t. for 30 min, carefully treated with water (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) followed by solvent evaportion, leaving a white solid which upon purification by column chromatography (eluent: EtOAc–hexane, 1:2) afforded **5a** (78 mg, 65%).

Mp 203.8–205.0 °C (CH_3CN).

IR (KBr): ν = 1668, 1584 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 13.30 (br s, 1H, NH), 7.31–7.19 (m, 5H, Ph), 7.15–7.08 (m, 4H, Ar), 6.84 (s, 1H, H-4), 5.24 (t, *J* = 5.7 Hz, 1H, OH), 4.46 (d, *J* = 5.7 Hz, 2H, CH_2).

MS (70 eV) *m/z* (%): 278 (M^+, 100), 247 (55).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.40; H, 5.03; N, 10.09.

5-(4-Cyanophenyl)-6-phenyl-(2*H*)-pyridazin-3-one (5b)

A mixture of the aldehyde **4d** (0.138 g, 0.5 mmol), NH_2OHHCl (0.052 g, 0.75 mmol) and TFA (10 mL) was refluxed (oil bath, 120 °C) for 3 h. After cooling, the solvent was removed at reduced pressure and the residue was poured into ice giving a solid that was filtered off and recrystallised from CH_3CN to give pure **5b** (89%).

Mp 247.0–248.5 °C (CH_3CN).

IR (KBr): ν = 1665, 1582 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 13.40 (br s, 1H, NH), 7.76 (d, *J* = 7.4 Hz, 2H, Ar), 7.33 (d, *J* = 7.4 Hz, 2H, Ar), 7.24 (m, 3H, Ph), 7.12 (m, 2H, Ph), 6.95 (s, 1H, H-4).

MS (70 eV) *m/z* (%): 273 (M^+, 100), 244 (30).

Anal. Calcd for $C_{17}H_{11}N_3O$: C, 71.74; H, 4.06; N, 15.38. Found: C, 71.76; H, 4.06; N, 15.34.

5-(4-Methoxycarbonylphenyl)-6-phenyl-(2*H*)-pyridazin-3-one (5c)

NaCN (0.05 g, 1 mmol) was added to a stirred solution of the aldehyde **4d** (0.138 g, 0.5 mmol) in EtOH (15 mL) and stirring was continued for 15 min. Then MnO_2 (8.9 g, 10 mmol) was added and stirring was continued for further 12 h. The suspension was then filtered through a pad of silica and the filtrate was concentrated under reduced pressure, giving a solid that was purified by column chromatography on silica gel to afford pure **5c** (80%).

Mp 215.0–216.1 °C (CH_3CN).

IR (KBr): ν = 1725, 1664, 1580 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 13.30 (br s, 1H, NH), 7.95 (d, *J* = 8.2 Hz, 2H, Ar), 7.33–7.14 (m, 7H, 5H Ph + 2H Ar), 7.02 (s, 1H, H-4), 3.94 (s, 3H, CH_3).

MS (70 eV) *m/z* (%): 306 (M^+, 100), 249 (40), 189 (54).

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.74; H, 4.06; N, 15.38. Found: C, 71.76; H, 4.06; N, 15.34.

5,6-Diphenyl-2-methylpyridazin-3-one (6)

5-bromo-2-methyl-6-phenylpyridazin-3-one (**2**) (0.42 g, 1.6 mmol) was mixed with phenylboronic acid (0.26 g, 2.2 mmol), $Pd(PPh_3)_4$ (0.018 g, 0.016 mmol) and K_2CO_3 (0.49 g, 5.08 mmol) in toluene–EtOH (2:1, 15 mL). The vessel was flushed with argon for 5 min and the mixture was then stirred and refluxed (120 °C) under argon until the starting material had disappeared (TLC monitoring). After cooling, the solution was evaporated to dryness under reduced pressure and the residue was purified by column chromatography on silica gel to give pure **6** (95%).

Mp 125.3–126.9 °C (CH_3CN).

IR (KBr): ν = 1652, 1590 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 9H, Ph + H-4), 7.11–7.05 (m, 2H, Ph), 3.91 (s, 3H, CH_3).

MS (70 eV) *m/z* (%): 262 (M^+, 100), 234 (80), 191 (94), 165 (60).

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