Pyridazines Part XXIII: Efficient Arylation at Position 5 of the 6-Phenyl-(2H)-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-(2H)-pyridazin-3-one system using a Suzuki cross-coupling reaction has been developed in the search for new platelet aggregation inhibitors.

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

The pyridazine system, which has been known for almost a century and may be considered as a biosisiter 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 [(2H)-pyridazin-3-ones] are recognised as versatile pharmacophores with a variety of biological activities 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-(2H)-pyridazin-3-ones and their 4,5-dihydro derivatives have attracted particular attention due to their important cardiovascular effects. For example, many of the pyridazines and 6-aryl-(2H)-pyridazin-3-ones obtained in our laboratory during this period are endowed with antihypertensive action or are powerful inhibitors of platelet aggregation.

Particularly, we have focused on the direct preparation of new platelet antiaggregation agents with a non c-AMP PDE III-based mechanism. These results have motivated us to prepare other 5-substituted-(2H)-pyridazin-3-ones, having alkylidene groups at position 5, which are potent antiplatelet agents. In continuation of this work, we have now designed a series of 5-aryl-6-phenyl-(2H)-pyridazin-3-ones, which permit a rapid pharmacomodulation 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).

Most syntheses of 5-substituted-(2H)-pyridazin-3-ones proceed via traditional methods, involving condensation of hydrazine with appropriate substituted lactones or 1,4-dicarbonyl compounds (Figure 2). Concretely, these synthetic routes to obtain 6-phenyl-(2H)-pyridazin-3-

Figure 1

Figure 2

We have therefore focused on the direct preparation of compounds 4 from readily obtainable, inexpensive 5-bromo-6-phenyl-(2H)-pyridazin-3-one (1) by palladium-catalysed carbon-carbon bond formation. The Suzuki cross-coupling-based 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 and have been especially popular due to their application in the preparation of complex natural products, heterocycles and in supramolecular chemistry. Curiously, very little appears to have been published on palladium-catalysed reactions of pyridazines. Although we recently reported the synthesis of several 5-vinyl- and 5-alkynyl-6-phenyl-(2H)-pyridazin-3-ones by the Stille, Heck or Sonogashira approaches, 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 aryloboronic acids but the difference in acidity between
these substrates and pyridazinones\textsuperscript{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\textsubscript{H})-pyridazin-3-ones 4a-f.

In a preliminary experiment we have used 5-bromo-6-phenyl-(2\textsubscript{H})-pyridazin-3-one (1)\textsuperscript{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-dimethoxyethane) and/or base (triethylamine, sodium bicarbonate, potassium carbonate, sodium or potassium hydroxide), and the 6-phenyl-5-iodo-(2\textsubscript{H})-pyridazin-3-one failed to improve the results.

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\textsuperscript{10} and X-ray crystallographic analyses,\textsuperscript{18} have shown that for the 5-substituted 6-phenyl-(2\textsubscript{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\textsubscript{H})-Pyridazin-3-one is about as acidic as phenol with a PK\textsubscript{a} of 10.5].

Table 1

<table>
<thead>
<tr>
<th>Base</th>
<th>Yield (%)</th>
<th>Base</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aHCO\textsubscript{3}</td>
<td>8</td>
<td>aCO\textsubscript{3}</td>
<td>10</td>
</tr>
<tr>
<td>aOH</td>
<td>–</td>
<td>OH</td>
<td>–</td>
</tr>
</tbody>
</table>

Determined by GC.

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.\textsuperscript{10,16} After some optimisation, we found that the reaction of the MOM-protected substrate 2 with arylboronic acids.

Figure 3

![Figure 3](image)

Figure 4

![Figure 4](image)

Table 2

<table>
<thead>
<tr>
<th>Compound Ar</th>
<th>Yield (%)</th>
<th>Compound Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Phenyl</td>
<td>98</td>
<td>4a</td>
<td>93</td>
</tr>
<tr>
<td>b 4-Cl-phenyl</td>
<td>89</td>
<td>4b</td>
<td>85</td>
</tr>
<tr>
<td>c 4-CH\textsubscript{3}-phenyl</td>
<td>96</td>
<td>4c</td>
<td>90</td>
</tr>
<tr>
<td>d 4-CHO-phenyl</td>
<td>92</td>
<td>4d</td>
<td>90</td>
</tr>
<tr>
<td>e 2-Furyl</td>
<td>94</td>
<td>4e</td>
<td>88</td>
</tr>
<tr>
<td>f 2-Thienyl</td>
<td>18/70\textsuperscript{b}</td>
<td>4f</td>
<td>10/65\textsuperscript{b}</td>
</tr>
</tbody>
</table>

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$_2$Cl$_2$, DMAP, (i-Pr)$_2$NEt, 0 ºC, 12 h; (ii) ArB(OH)$_2$, Pd(PPh$_3$)$_4$, K$_2$CO$_3$, EtOH–toluene, reflux, 2–6 h; (iii) 6 N HCl, reflux, 6 h; (iv) a) ArB(OH)$_2$, Pd(PPh$_3$)$_4$, K$_2$CO$_3$, 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, we carried out the reaction in 1,2-dimethoxethane (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-(2H)-pyridazin-3-ones 4 starting from the 2-methoxymethyl derivative of readily available 5-bromo-6-phenyl-(2H)-pyridazin-3-one 1. Further investigations are now in progress in order to obtain new 5-aryloyl 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 internal standard.

### Table 3 Spectroscopic Data of Pyridazin-3-ones 3a–f

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mp (°C)</th>
<th>IR (KBr) (cm$^{-1}$)</th>
<th>MS m/z (%)</th>
<th>$^1$H NMR (CDCl$_3$) δ, J (Hz)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Oil</td>
<td>1562, 1590</td>
<td>292 (M$^+$, 27), 249 (100)</td>
<td>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$_3$)</td>
</tr>
<tr>
<td>b</td>
<td>136.0–136.5$^a$</td>
<td>1656, 1592</td>
<td>326 (M$^+$, 8), 225 (100)</td>
<td>7.40–7.30 (m, 5H, Ph), 7.17 (d, $J = 8.3$, 2H, Ar), 7.04 (d, $J = 8.0$, 2H, Ar), 6.95 (s, 1H, H-4), 5.55 (s, 2H, CH$_2$), 3.55 (s, 3H, CH$_3$)</td>
</tr>
<tr>
<td>c</td>
<td>Oil</td>
<td>1667, 1588</td>
<td>262 (M$^+$, 100)</td>
<td>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$_3$)</td>
</tr>
<tr>
<td>d</td>
<td>Oil</td>
<td>1710, 1664</td>
<td>320 (M$^+$, 12), 219 (100)</td>
<td>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$_3$)</td>
</tr>
<tr>
<td>e</td>
<td>102.0–102.7$^a$</td>
<td>1661, 1589</td>
<td>282 (M$^+$, 16), 181 (100)</td>
<td>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$_3$)</td>
</tr>
<tr>
<td>f</td>
<td>Oil</td>
<td>1671, 1592</td>
<td>298 (M$^+$, 15), 197 (100)</td>
<td>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$_3$)</td>
</tr>
</tbody>
</table>

Recrystallised from acetonitrile.

NMR data were recorded at 300 MHz.
7.21 (s, 1H, H-4), 5.45 (s, 2H, CH\textsubscript{2}), 3.42 (s, 3H, CH\textsubscript{3}).

IR (KBr): needles; mp 103.0°C.

A mixture of bromopyridazinone 5-Bromo-2-methoxymethyl-6-phenylpyridazin-3-one \(2\) (1.70 g, 6.77 mmol), 4-\(N,N\)-dimethylaminopyridine (0.10 g) and diisopropylethylamine (1.20 g, 1.62 mL, 10.11 mmol) in anhyd CH\textsubscript{2}Cl\textsubscript{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): \(v = 1669\) (CO), 1748 (C=O–C) 1588 (aromatics) cm\(^{-1}\).

\(^{1}H\) NMR (300 MHz, CDCl\textsubscript{3}); \(\delta = 7.63\) (m, 2H, Ar), 7.40 (m, 3H, Ar), 7.21 (s, 1H, H-4), 5.45 (s, 2H, CH\textsubscript{2}), 3.42 (s, 3H, CH\textsubscript{3}).

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

Recrystallised from acetonitrile.

NMR data were recorded at 300 MHz.

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, and the residue was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3×25
continued for 15 min. Then MnO₂ (8.9 g, 10 mmol) was added and NaCN (0.05 g, 1 mmol) was added to a stirred solution of the aldehyde (5c) mp 203.8–205.0 °C (CH₃CN).

IR (KBr): ν = 1668, 1584 cm⁻¹

1H NMR (250 MHz, CDCl₃): 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, CH₃).

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

Anal. Calcd for C₁₇H₁₄N₂O₂: C, 73.37; H, 5.07; N, 10.07. Found: C, 71.76; H, 4.06; N, 15.34.

Acknowledgement

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References

1. (a) Part of this work was presented at the 7th International Symposium on the Chemistry and Pharmacology of Pyridazines, Santiago de Compostela, Spain, September 2000. (b) For the previous paper in this series, see: Sotelo, E.; Pita, B.; Raviñañez, I.; Raviñanañez, E.; Fontenla, J.; Orallo, F.; Calleja, J. M. Eur. J. Med. Chem. 1990, 25, 141.


