Pyridazines. Part 26:[1] Efficient and Regioselective Pd-Catalysed Arylation of 4-Bromo-6-chloro-3-phenylpyridazine

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Abstract: The regioselective arylation at position 4 of 4-bromo-6-chloro-3-phenylpyridazine has been performed using a Suzuki cross-coupling reaction. This route allows access to a wide-ranging series of pharmacologically useful pyridazine derivatives and confirms the usefulness of chloropyridazines as a masking group for the carbonyl moiety in cross-coupling reactions involving 5-bromo-3(2*H*)-pyridazinones.

Key words: arylations, palladium, catalysis, pyridazine

The pyridazine nucleus, which can be considered a bioisostere of benzene and other heterocycles, has proved to be a versatile system in Medicinal Chemistry. Among the pyridazine derivatives developed in recent years as drugs and pharmacological tools, 3(2*H*)-pyridazinones, aminopyridazines and hydrazinopyridazines are well recognised pharmacophores that show a wide range of biological activities (Figure 1).[2] Despite the useful nature of pyridazines, there are only a limited number of synthetic approaches to achieve substitution on these electron-deficient rings and, therefore, functionalisation of the pyridazine nucleus continues to be of synthetic interest. A number of methods have recently been described in the literature and, of these, reactions involving organometallics have proved to be a powerful tool for the preparation of the desired compounds. Several publications have dealt with the use of bromo- and iodopyridazines in Pd-catalysed reactions.[3–8]

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.[9] As a consequence of α and γ activation of heteroaryl halides, Pd-catalysed chemistry may occur regioselectively at the activated positions, a phenomenon rarely seen in carbocyclic aryl halides.[10–12] Very recently, Lemière[13] and Wermuth[14] described excellent preparative methods based on the oxidative insertion of palladium into the C-Cl bond on a pyridazine ring using tetrakis(triphenylphosphine)palladium(0) as a catalyst. These studies highlighted the activation of 3- and 6-chloropyridazines toward such reactions. However, to the best of our knowledge, there is only a report in the literature[15] describing the regioselectivity in palladium-catalysed cross-coupling reactions involving dihalopyridazines and their synthetic utilisation have not been sufficiently exploited.

While several previous reports have described palladium-catalysed reactions involving pyridazines or pyridazinones, our goal was the development of a general and highly flexible route based on the different reactivities of the halides (Br/Cl at the 4- and 6-positions of the heterocycle, respectively) toward oxidative addition in palladium chemistry. In this paper we describe a convenient and highly versatile palladium-assisted approach to the preparation of chemical libraries of 4-aryl-6-chloropyridazines **3**, 3(2*H*)-pyridazinones **4**, 6-aminopyridazines **5**, 6-hy-

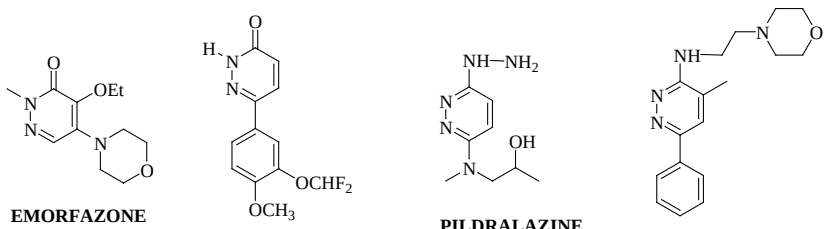

Figure 1 Several pharmacologically useful pyridazine derivatives

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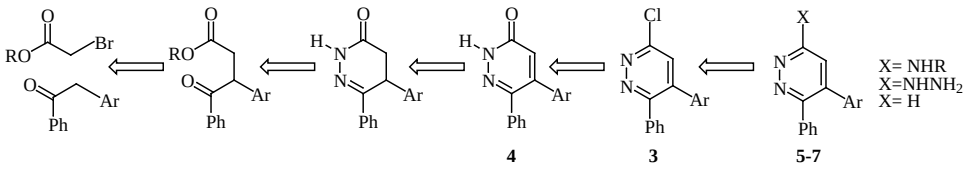
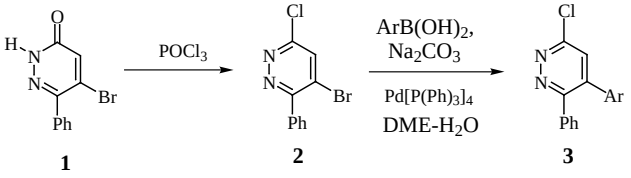


Scheme 1 Traditional retrosynthetic approach to compounds **3**-**7**

drazinopyridazines **6** and pyridazines **7**. The conventional synthesis of such compounds is possible in five steps (Scheme 1), but this is a somewhat lengthy process[16] and such approaches do not allow rapid access to a variety of structural analogues. We therefore focused on direct methods of preparation involving palladium-catalysed carbon-carbon bond formation with organoboranes, which permit a rapid pharmacomodulation of this series of compounds.

In this area we recently described the palladium-assisted alkenylation,[17] alkynylation[17] and arylation[18] of 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1**. During the course of these studies we observed that the NH group of the lactam function completely inhibits palladium-catalysed reactions. Indeed, prior to submitting the 3(2*H*)-pyridazinone to the catalytic cycle it is essential to protect the NH group in these compounds. Oxidative insertion of palladium into the C-Cl bond requires a higher energy than the case of a C-Br bond and, in addition, 3(2*H*)-pyridazinones are not particularly reactive - it is usually necessary to transform them into a suitable derivative, such as a 2-alkylpyridazinone, prior to reaction. For these reasons, we decided to explore the utility of 6-chloropyridazine as a protecting group for the enolizable lactam (C=O) moiety in compound **1**. The reverse hydrolysis process has seldom been used, probably because of the fact that most 6-chloropyridazines are prepared from the corresponding 3(2*H*)-pyridazinones, and so their utility to mask the carbonyl group in troublesome reactions has not been exploited in terms of synthetic procedures. This alternative approach has significant advantages in the synthesis of pyridazine derivatives **4**-**7**.



Scheme 2

As shown in Scheme 2, the readily obtainable 5-bromo-6-phenyl-3(2*H*)-pyridazinone **1**[17] was converted into 4-bromo-6-chloro-3-phenylpyridazine **2** in high yield by direct chlorination using phosphorus oxychloride.[19] We then proceeded to study the arylation of **2** using various substituted arylboronic acids. After some optimisation of the experimental conditions we found the cross-coupling reaction of **2** under classical Suzuki conditions[20] [5% tetrakis(triphenylphosphine)palladium(0) as catalyst, 2 M aqueous sodium carbonate as base, 1 equivalent of the appropriate boronic acid, toluene as solvent] to work smoothly. The transformation proceeded almost exclusively at position 5 of the heterocyclic nucleus to give the 4-arylated-6-chloropyridazines **3** in moderate to excellent yields (70-95%).[21]

The use of 1,2-dimethoxyethane (DME) as solvent together with aqueous Na_2CO_3 is regarded as a very convenient system for troublesome Suzuki couplings[22] and we therefore decided to study the cross-coupling reaction of **2** under these conditions. These experiments (Table) allowed us to obtain 4-aryl-6-chloro-3-phenylpyridazines **3** in similar yields and with shorter reaction times. The use of other bases [K_3PO_4, NaOH, $Ba(OH)_2$], solvents (DMF, dioxane, toluene/ethanol) or catalysts (Pd_2dba_3/P-*t*Bu_3) was also explored (using **2** and the phenyl and 4-methylphenylboronic acids) but yields were no higher than those obtained under the conventional conditions.

Table Synthesis of 4-Aryl-6-chloro-3-phenylpyridazines **3**.[27]

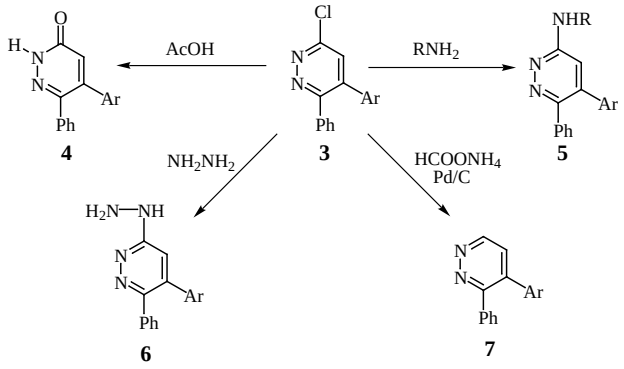
Compound	R	Mp °C (solvent)	Yield (%)
3a	Ph	111–112 (*iso*-PrOH)	90
3b	4-CH_3-Ph	126–127 (*iso*-PrOH)	95
3c	4-Cl-Ph	139–141 (*iso*-PrOH)	70
3d	4-OCH_3-Ph	150–152 (*iso*-PrOH)	96
3e	2-Furan	129–130 (EtOH)	83
3f	2-Thiophene	141–143 (EtOH)	85
3g	4-CHO-Ph	116-118 (MeOH)	73

It is worth mentioning here that, although the two procedures described above take place under aqueous conditions, we did not detect any by-products due to the hydrolytic degradation of the 6-chloropyridazines **2** or **3**. In accordance with previous studies[9,20] we obtained the best yields in the Suzuki coupling when either toluene or DME was used as solvent in reactions with boronic acids bearing electron-donating substituents (OCH_3, CH_3). Long reaction times arising from the use of less reactive boronic acids (4-Cl-Ph and 4-CHO-Ph) led to decreases in the yields of the coupling products, probably due to hydrolytic deboronation or slow transmetalation. For example, the use of 4-chlorophenylboronic acid led to mixtures of products from which only a moderate yield (70%) of **3c** was obtained. The heteroarylboronic acids show compa-

rable reactivity. In order to assess the scope of our new approach, we performed several experiments using a variable excess of the boronic acid (1.1-1.3 equivalent), a process that gave the 4-arylated-6-chloropyridazines **3** in moderate yields (70-85%). The use of a large excess of the organoboron compound leads to reaction mixtures arising from the formation of mono- as well as diarylpyridazines, as evidenced by TLC, ^{1}H NMR spectroscopy and mass spectrometry.

The total regioselectivity obtained in the biaryl cross-coupling reaction on **2** is not wholly expected considering the high reactivity previously shown by the C-Cl bond at position 6 of the pyridazine nucleus in the Pd-insertion process.[13,14] We can explain this selectivity by considering the fact that, although oxidative addition into the C-Cl bond occurs easily, the energy involved in this transformation is even higher than in the case of a similar process involving the C-Br bond. It is this major energy difference that allows the use the 6-chloropyridazines as a masking group for the carbonyl moiety in palladium-assisted cross-coupling reactions of 5-bromo-3(2*H*)-pyridazinones. The selective arylation at the 4-position of 4-bromo-6-chloro-3-phenylpyridazine is considered to be synthetically useful because the chloro-substituent at position 6 of the pyridazine ring can be easily converted to give a wide range of functionalities.

Once the coupling conditions had been optimised we successfully completed the transformation of 6-chloropyridazines **3**[21] into 3(2*H*)-pyridazinones **4**,[23] 6-aminopyridazines **5**,[24] 6-hydrazynopyridazines **6**[25] or pyridazines **7**[26] following the previously described procedures (Scheme 3).[16] The application of this procedure to other dihalopyridazines is currently under investigation. We are also applying this methodology to the preparation of chemical libraries of compounds **3**-**7** using combinatorial techniques.



Scheme 3

In summary, we have developed a practical, efficient and regioselective palladium-assisted procedure based on the different reactivity of halides toward oxidative addition of palladium species'. The chemoselectivity observed demonstrates the synthetic usefulness of the 6-chloropyridazine moiety as a convenient masking group for the carbonyl function in Suzuki arylations. This procedure is superior to existing processes and has allowed us to access, in a clearly shorter synthetic sequence, several pharmacologically useful pyridazine derivatives.

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(19) 4-Bromo-6-chloro-3-phenylpyridazine **2**: 89%, mp: 111-112 °C (dec.), *iso*-PrOH. IR (KBr): 1590, 1480 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): 8.44 (s, 1 H, CH), 7.70 (m, 2 H, Aromatics), 7.54 (m, 3 H, Aromatics) ppm.
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(21) Cross-coupling Reactions, General Procedure: 5-Bromo-3-chloro-6-phenylpyridazine **2** (0.25 g, 0.93 mmol) was mixed with the arylboronic acid (0.93 mmol), $Pd(PPh_3)_4$ (5 mg, 0.006 mmol) and Na_2CO_3 (0.49 g, 5.08 mmol) in 30 mL of a 3:1 mixture of DME–H_2O. The mixture was flushed with

argon for 5 min and then stirred and heated at reflux (oil bath 90 °C) under argon until the starting material had disappeared (8-12 h). The mixture was allowed to cool and concentrated to dryness under reduced pressure. The residue was extracted into CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4) and then purified by column chromatography on silica gel to afford the 6-chloropyridazines **3**, which were recrystallised from the appropriate solvent (Table).
Selected physical and spectral data for compounds **3**. **3a**: 90%, mp: 111-112 °C (dec.), *iso*-PrOH. IR (KBr): 1563, 1092, 695 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 8.61 (s, 1 H, CH), 8.23 (m, 2 H, Aromatics), 7.79 (m, 2 H, Aromatics), 7.57 (m, 6 H, Aromatics) ppm. **3b**: 95%, mp: 126-127 °C, *iso*-PrOH. IR (KBr): 1559, 1089, 696 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 8.54 (s, 1 H, CH), 8.14 (d, *J* = 8.0 Hz, 2 H, Aromatics), 7.76 (m, 2 H, Aromatics), 7.55 (m, 3 H, Aromatics), 7.37 (d, *J* = 8.0 Hz, 2 H, Aroma tics), 2.38 (s, 3 H, CH_3) ppm. **3d**: 95%, mp: 150-152 °C *iso*-PrOH. IR (KBr): 1560, 1090, 697 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 8.39 (s, 1 H, CH), 8.08 (d, *J* = 8.8 Hz, 2 H, Aromatics), 7.61 (m, 2 H, Aromatics), 7.41 (m, 3 H, Aromatics), 6.97 (d, *J* = 8.8 Hz, 2 H, Aromatics), 3.70 (s, 3 H, OCH_3) ppm.

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(23) 3(2*H*)-Pyridazinones **4** were prepared heating at reflux **3a-f** in neat acetic acid during 3-7 h. **4a**: 86%, mp: 178.5-180.6 °C, Acetonitrile. IR (KBr): 3000, 1668, 1589cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 11.58 (bs, 1 H, NH), 7.38-7.20 (m, 10 H Aromatics), 7.01 (s, 1 H, H_4) ppm. **4e**: 84%, mp: 235.0-235.5 °C, *iso*-PrOH. IR (KBr): 3000, 1662, 1580 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 12.05 (bs, 1H, NH), 7.48-7.33 (m, 7 H, 5 H Aromatics + 1 H furan + H_4), 6.28 (dd, *J* = 3.5, 1.8 Hz, 1 H, furan), 5.64 (d, *J* = 3.5 Hz, 1 H; furan) ppm.

(24) Aminopyridazines **5** were prepared heating at reflux **3a-f** in presence of the appropriate amine (3 equivalents) in ethanol (24-72 h). 3,4-Diphenyl-6-(2-methoxyethylamino)pyridazine **5a**: 78%, (72 h) mp: 199-201 °C, *iso*-PrOH. IR (KBr): 3000, 1590 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 7.69-7.21 (m, 10 H, Aromatics), 6.94 (s, 1 H, H_4), 3.64 (t, *J* = 7.1 Hz, 2 H, CH_2), 3.35 (s, 3 H, CH_3), 3.29 (t, *J* = 7.1 Hz, 2 H, CH_2) ppm.

(25) Hydrazinopyridazines **6** were prepared heating at reflux **3a-f** in presence of 3 equivalents of hydrazine hydrate in ethanol (3-4 h). 3,4-Diphenyl-6-hydrazinopyridazine **6a**: 89%, mp: 153-155 °C, *iso*-PrOH.[28] IR (KBr): 3500-300, 1576 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 8.12 (m, 3 H, Aromatics), 7.67 (m, 2 H, Aromatics), 7.54 (s, 1 H, CH), 7.51 (m, 6 H, Aromatics), 6.08 (2, 1 H, NH), 3.48 (s, 2 H, NH_2) ppm.

(26) Pyridazines **7** were prepared by reductive dechlorination of **3a-f** ($HCOONH_4$/Pd-C, MeOH). 3,4-diphenylpyridazine **7a**: 88%, mp: 106-107 °C, *iso*-PrOH.[29] IR (KBr): 1590 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 9.21 (d, *J* = 5.2 Hz, 1 H, CH), 7.50 (d, *J* = 5.2 Hz, 1 H, CH), 7.46 (m, 10 H, Aromatics) ppm.

(27) Complete details of the synthesis and spectral characteristics of the compounds obtained will be published elsewhere in a full paper. All compounds gave satisfactory microanalytical (C, H, N ± 0.4%) and spectral data (^1H, ^{13}C, FTIR, MS). Yields given correspond to isolated pure compounds.

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