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A new method for the synthesis of 3-aryl-6-(2-pyrrolyl)pyridazines

Chuanjun Song *, Peng Zhao, Yan Liu, Hui Liu, Wenjia Li, Shuai Shi, Junbiao Chang *

Department of Chemistry, Zhengzhou University, 100 Science Avenue, Zhengzhou 450001, China

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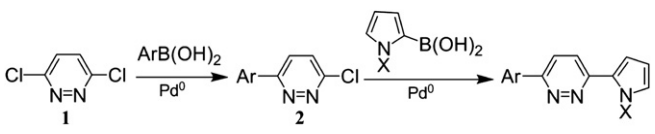
ABSTRACT

A new method for the synthesis of 3-halo-6-(*N*-tosyl-2-pyrrolyl)pyridazine **7** was developed. Suzuki cross-coupling reactions of **7** with arylboronic acids and in situ de-tosylation gave a variety of novel 3-aryl-6-(2-pyrrolyl)pyridazines. It found that protection of the pyrrolyl moiety was necessary for efficient coupling reaction.

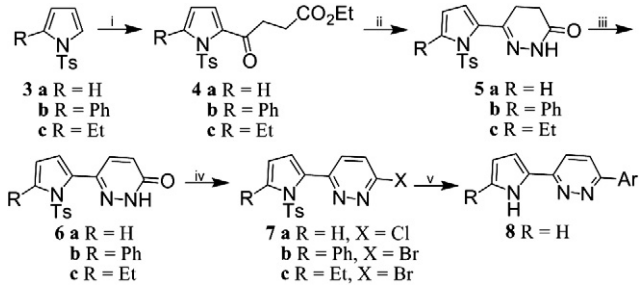
1. Introduction

3-Aryl-6-(2-pyrrolyl)pyridazines are pharmaceutically important molecules.[1-6] However, there are very few literature reports describing their synthesis. Probably the most straightforward approach involves the sequential palladium catalyzed Suzuki cross-coupling reaction of 3,6-dichloropyridazine **1** with arylboronic acid followed by coupling with *N*-protected 2-pyrrolylboronic acid, although the overall yield is generally very low (Scheme 1).[1,5,7] This is mainly due to the competitive cross-coupling reaction of 3-aryl-6-chloropyridazine **2** with a second molecule of arylboronic acid to generate symmetrical 3,6-diarylpyridazine. Also, access to the pyrrolylboronic acid moiety is not easy.[8–10] Other reported methods for the synthesis of 3/6-(2-pyrrolyl)pyridazine-containing molecules include Sauer's synthesis of 3-(2-pyrrolyl)-5-tributylstannylpyridazines by a regioselective [4+2] cycloaddition reaction between 3-(2-pyrrolyl)-1,2,4,5-tetrazine and ethynyltributyltin.[11] However, the reaction is slow (3–10 days) and the yield for the synthesis of the tetrazine starting material is low. A small amount of 3,4-disubstituted pyridazine was also obtained. In an attempt to react pyrrolylmagnesium bromide with 3,6-dichloropyridazine **1**, Jones and Whitmore isolated 3-chloro-6-(2-pyrrolyl)-pyridazine, which was reluctant to react further to give the desired 3,6-dipyrrolylpyridazine.[12]



Scheme 1.

Condensation of γ-keto esters with hydrazine followed by aromatization and treatment of the resulting pyridazin-3-ones with phosphorus oxychloride gave 3-chloropyridazines, which could react further to give 3,6-disubstituted pyridazines.[13] To our surprise, although several groups have reported the synthesis of 6-(2-pyrrolyl)pyridazin-3-one,[14–16] further elaboration to the corresponding pyrrolylpyridazine derivatives has not been explored. Previously, we developed a new pyrrole acylation method using carboxylic acids and TFAA,[17] we now report the application of this methodology to the synthesis of 3-halo-6-(*N*-tosyl-2-pyrrolyl) pyridazine **7** (Scheme 2) and the subsequent transformation into 3-substituted-6-(2-pyrrolyl)pyridazines.



Scheme 2. Reagents and conditions: (i) monoethyl succinate, TFAA, DCE; (ii) $NH_2NH_2{\cdot}H_2O$, AcOH, reflux; (iii) SeO_2, dioxane, reflux; (iv) $POCl_3$ or $POBr_3$–toluene, reflux; (v) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene–MeOH, 80 °C, 12 h.

* Corresponding authors. Tel.: +86 0371 67781788 (C.S.); tel.: +86 0371 67783017 (J.C.); e-mail addresses: chjsong@zzu.edu.cn (C. Song), changjunbiao@zzu.edu.cn (J. Chang).

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2. Results and discussion

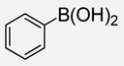
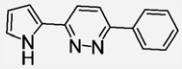
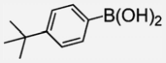
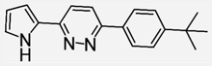
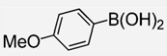
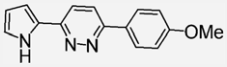
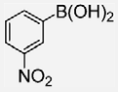
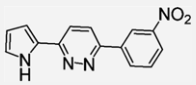
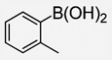
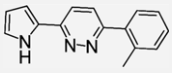
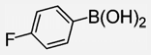
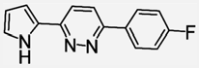
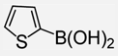
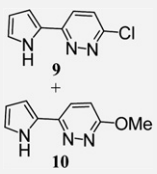
Initial optimization was carried out with *N*-tosylpyrrole **3a**. As shown in Scheme 2, the pyrrole acylation product **4a** was condensed with hydrazine hydrate to give **5a** in 69% isolated yield. DDQ oxidation of **5a**, either under reflux or at ambient temperature, led to the formation of pyridazin-3-one **6a** in only moderate yield. However, good yield was obtained when selenium dioxide was employed as the oxidant. Treatment of **6a** with phosphorus oxychloride gave the desired 3-chloro-6-(*N*-tosyl-2-pyrrolyl)pyridazine **7a** in excellent yield. Applying the same sequence of transformations to 2-phenyl-*N*-tosylpyrrole **3b**, 3-bromo-6-(5-phenyl-*N*-tosyl-2-pyrrolyl)pyridazine **7b** was synthesized in good overall yield. 3-Chloro-6-(5-phenyl-*N*-tosyl-2-pyrrolyl)pyridazine (**7**, R=Ph, X=Cl) could also be obtained by treating the pyridazin-3-one **6b** with phosphorus oxychloride, but only in a disappointing 10% yield. However, an excellent yield of the equivalent 3-bromopyridazine **7b** was obtained when phosphorus oxybromide was applied. It proved problematic, although still possible, to convert 2-ethyl-*N*-tosylpyrrole **3c** to the corresponding 3-bromopyridazine **7c** using our sequence of transformations. Condensation of the acylation product **4c**, which was obtained in good yield, with hydrazine hydrate gave poor conversion and prolonged reaction times only led to decreased yields. At best, the dihydropyridazin-3-one **5c** was isolated in 35% yield, together with 20% recovered starting material. The isolated yields for the following two steps were also quite low (35% and 20%, respectively).

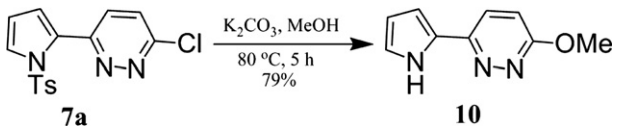
Next, using 3-chloro-6-(*N*-tosyl-2-pyrrolyl)pyridazine **7a** as an example, the Suzuki cross-coupling reaction[18] with various arylboronic acids was investigated. A mixture of the chloride **7a**, phenylboronic acid, potassium carbonate and a catalytic amount (5 mol %) of tetrakis(triphenylphosphine) palladium was refluxed for 12 h until TLC indicated the reaction was completed. The de-tosylated cross-coupling product 3-phenyl-6-(2-pyrrolyl) pyridazine (i.e., **8**, Ar=Ph) was obtained in 87% isolated yield. Employing the cyclopalladated ferrocenylimine catalyst developed by Wu et al.,[19] or change of base (K_3PO_4, NaOH) gave similar results, thus we employed the first described conditions for the rest of our study. The results of cross-couplings with other boronic acids are listed in Table 1.

As expected, an electron-donating substituent on the phenyl ring (entries 2 and 3) led to higher yields than electron-withdrawing groups (entry 4). Steric effects also played a significant role, as could be seen from the decreased yield of 2-methylphenylboronic acid (entry 5) compared to phenylboronic acid (entry 1). It is perhaps not surprising that thiophenyl-2-boronic acid did not undergo cross-coupling reaction, but led to formation of 3-chloro-6-(2-pyrrolyl)pyridazine **9** and 3-methoxy-6-(2-pyrrolyl)-pyridazine **10** in 44% and 21% isolated yield, respectively.

Following known literature procedure,[12] other pyrrolylpyridazine derivatives could be obtained by nucleophilic aromatic substitution of the chloride in **9**, but rather slowly. For example, compound **10** was obtained in good yield only after prolonged reflux (72 h) in methanol when sodium methoxide was used as the nucleophile. We reasoned that an electron-withdrawing group should greatly facilitate this process. Indeed, reaction of the tosyl-protected compound **7a** with methanol in the presence of potassium carbonate was completed in 5 h and resulted in the formation of **10** in 79% isolated yield (Scheme 3). Removal of the tosyl protecting group is usually carried out under strongly basic or acidic conditions.[20] We assumed that the facile in situ de-tosylation observed during the Suzuki cross-coupling reactions of **7a** (Table 1) and during the nucleophilic substitution reaction shown in Scheme 3 was due to the strong electron-withdrawing nature of the pyridazine moiety.[21]

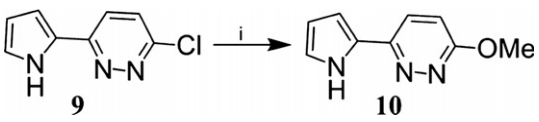
Table 1
Results of Suzuki cross-coupling reactions of chloride **7a** with boronic acids

Entry	Boronic acid	Product	Yield (%)
1			87
2			86
3			86
4			75
5			66
6			38
7			44 21



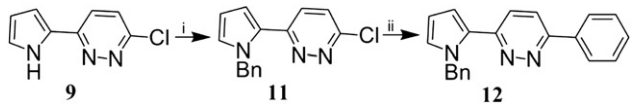
Scheme 3.

Next, the cross-coupling reaction between 3-chloro-6-(2-pyrrolyl) pyridazine **9** and 4-methoxyphenylboronic acid was attempted. However, no coupling product was observed. Instead, compound **10** resulting from nucleophilic aromatic substitution of the chloride with methoxy group was obtained in quantitive yield (Scheme 4).



Scheme 4. Reagents and conditions: *p*-methoxyphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene–MeOH, 80 °C, 12 h, quant.

We then prepared the *N*-benzyl derivative **11**, Suzuki cross-coupling of which with phenylboronic acid proceeded smoothly to give compound **12** in 82% isolated yield (Scheme 5). This, together with the previous results, indicated that protection of the pyrrolyl moiety was necessary for efficient cross-coupling reaction.



Scheme 5. Reagents and conditions: (i) NaH, BnBr, THF, rt, 72 h, 41%; (ii) phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene–MeOH, 80 °C, 14.5 h, 82%.

3. Conclusion

In summary, a new method for the synthesis of 3-halo-6-(*N*-tosyl-2-pyrrolyl)pyridazine **7** based on pyrrole acylation has been developed. Suzuki cross-coupling reactions of 3-chloro-6-(*N*-tosyl-2-pyrrolyl)pyridazine **7a** with arylboronic acids were studied and gave, with in situ de-tosylation, a variety of novel 3-aryl-6-(2-pyrrolyl)pyridazines in good yields.

4. Experimental

4.1. Ethyl 4-oxo-4-(*N*-tosyl-2′-pyrrolyl)butanoate 4a[22]

A solution of *N*-tosylpyrrole **3a** (7.86 g, 35 mmol), trifluoroacetic anhydride (26.4 mL, 190 mmol) and monoethyl succinate (13.82 g, 95 mmol) in DCE (200 mL) was heated to reflux for 14 h. After being allowed to cool to rt, water (30 mL) was added dropwise to quench the reaction. The separated aqueous phase was extracted with DCM (3×20 mL). The combined organic extracts were dried (Na_2SO_4), filtrated and evaporated in vacuo. The residue was purified by column chromatography on silica gel with petroleum ether–EtOAc (10:1) as eluent to give acylpyrrole **4a** (10.55 g, 85%) as a colourless solid; mp 83–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.88 (2H, d, *J*=8.4 Hz), 7.79 (1H, dd, *J*=3.2, 1.7 Hz), 7.30 (2H, d, *J*=8.4 Hz), 7.12 (1H, dd, *J*=3.2, 1.7 Hz), 6.34 (1H, t, *J*=3.2 Hz), 4.08 (2H, q, *J*=7.1 Hz), 3.04 (2H, t, *J*=7.0 Hz), 2.62 (2H, t, *J*=7.0 Hz), 2.41 (3H, s) and 1.20 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 186.3 (CO), 172.6 (CO), 144.8, 135.8, 132.7 (all C), 130.2 (CH), 129.3 (2×CH), 128.3 (2×CH), 123.6, 110.3 (both CH), 60.6, 33.9, 28.3 (all CH_2), 21.7 and 14.1 (both CH_3).

4.2. Ethyl 4-oxo-4-(5′-phenyl-*N*-tosyl-2′-pyrrolyl)butanoate 4b

Compound **4b** was synthesized according to the procedure described for the synthesis of **4a** by refluxing a mixture of **3b**, TFAA and monoethyl succinate in DCE for 22 h, in 68% isolated yield as a brown oil; ν_{max}/cm^{-1} 1733 (CO), 1690 (CO), 1370 and 1174; ^{1}H NMR (300 MHz, $CDCl_3$) 7.32–7.11 (7H, m), 7.04 (2H, d, *J*=8.1 Hz), 6.84 (1H, d, *J*=3.3 Hz), 6.05 (1H, d, *J*=3.3 Hz), 4.08 (2H, q, *J*=7.2 Hz), 3.18 (2H, t, *J*=6.9 Hz), 2.72 (2H, t, *J*=6.9 Hz), 2.29 (3H, s) and 1.19 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 191.6 (CO), 173.1 (CO), 145.1, 144.8, 139.1, 135.2 (all C), 130.0 (2×CH), 129.1 (2×CH), 128.2 (CH), 127.7 (4×CH), 122.0, 114.9 (both CH), 60.8, 36.6, 28.9 (all CH_2), 21.6 and 14.1 (both CH_3); *m*/*z* (ESI) 448 (M^++Na, 13%), 426 (M^++H, 100), 398 (12) and 372 (10) [found: M^++H, 426.1377. $C_{23}H_{24}NO_5S$ requires 426.1375].

4.3. Ethyl 4-oxo-4-(5′-ethyl-*N*-tosyl-2′-pyrrolyl)butanoate 4c

Compound **4c** was synthesized according to the procedure described for the synthesis of **4a** by reacting a mixture of **3c**, TFAA and monoethyl succinate in DCE at rt for 12 h, in 75% isolated yield as a colourless solid; mp 54–56 °C; ν_{max}/cm^{-1} 1731 (CO), 1690 (CO), 1490, 1366, 1322, 1175 and 1109; ^{1}H NMR (300 MHz, $CDCl_3$) 7.87 (2H, d, *J*=8.1 Hz), 7.24 (2H, d, *J*=8.1 Hz), 6.81 (1H, d, *J*=3.6 Hz), 5.97 (1H, d, *J*=3.6 Hz), 4.04 (2H, q, *J*=6.9 Hz), 3.03 (2H, t, *J*=6.9 Hz), 2.84 (2H, q, *J*=7.2 Hz), 2.62 (2H, t, *J*=6.9 Hz), 2.34 (3H, s) and 1.21–1.13 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 189.5 (CO), 172.8 (CO), 146.7, 144.7, 136.6, 135.8 (all C), 129.5 (2×CH), 127.6 (2×CH), 121.1, 110.3 (both CH), 60.5, 35.6, 28.5, 22.0 (all CH_2), 21.6, 14.1 and 12.9 (all CH_3); *m*/*z* (ESI) 400 (M^++Na, 100%) and 378 (M^++H, 5) [found: M^++Na, 400.1195. $C_{19}H_{23}NNaO_5S$ requires 400.1195].

4.4. 6-(*N*-Tosyl-2′-pyrrolyl)-4,5-dihydropyridazin-3-one 5a

A mixture of acylpyrrole **4a** (4.14 g, 11.9 mmol), hydrazine hydrate (10 mL, 165 mmol) and acetic acid (30 mL) was heated to reflux for 23 h, then evaporated in vacuo. The residue was washed with water (3×5 mL) and filtrated. The filter cake was washed with EtOAc (3×5 mL) to give *dihydropyridazin-3-one* **5a** (2.61 g, 69%) as a colourless solid; mp 222–225 °C; ν_{max}/cm^{-1} 3200 (NH), 1673 (CO), 1353, 1172, 1146 and 1066; ^{1}H NMR (300 MHz, DMSO) 10.90 (1H, s), 7.78 (2H, d, *J*=8.3 Hz), 7.56 (1H, dd, *J*=3.4, 1.7 Hz), 7.39 (2H, d, *J*=8.3 Hz), 6.55(1H, dd, *J*=3.4, 1.7 Hz), 6.38 (1H, t, *J*=3.4 Hz), 2.77–2.72 (2H, m) and 2.43–2.38 (5H, m); ^{13}C NMR (75 MHz, DMSO) 166.9 (CO), 144.9, 143.6, 135.3, 131.6 (all C), 129.7 (2×CH), 127.6 (2×CH), 126.0, 117.3, 112.4 (all CH), 26.3, 25.6 (both CH_2) and 21.1 (CH_3); *m*/*z* (ESI) 340 (M^++Na, 10%) and 318 (M^++H, 100) [found: M^++H, 318.0831. $C_{15}H_{16}N_3O_3S$ requires 318.0912].

4.5. 6-(5′-Phenyl-*N*-tosyl-2′-pyrrolyl)-4,5-dihydropyridazin-3-one 5b

Compound **5b** was synthesized according the procedure described for the synthesis of **5a** by refluxing a mixture of **4b**, hydrazine hydrate and acetic acid for 36 h. The crude product was purified by column chromatography to give **5b** (49%) as a pale solid; mp 197–201 °C; ν_{max}/cm^{-1} 3323 (NH), 1670 (CO), 1348, 1287, 1154, 1132 and 1028; ^{1}H NMR (300 MHz, DMSO-d_6) 12.32 (1H, m), 10.84 (1H, s), 7.49–7.41 (7H, m), 7.26 (2H, d, *J*=8.4 Hz), 7.01 (1H, d, *J*=2.7 Hz), 2.88 (2H, t, *J*=8.1 Hz), 2.42 (2H, t, *J*=8.1 Hz) and 2.31 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) 167.1 (CO), 143.1, 142.9, 140.4, 137.0 (all C), 129.9 (2×CH), 129.5 (2×CH), 128.9 (CH), 128.8 (C), 127.6 (2×CH), 126.2 (2×CH), 121.7 (C), 112.1 (CH), 26.0, 21.8 (both CH_2) and 20.9 (CH_3); *m*/*z* (ESI) 416 (M^++Na, 100) and 394 (M^++H, 93) [found: M^++H, 394.1223. $C_{21}H_{20}N_3O_3S$ requires 394.1225].

4.6. 6-(5′-Ethyl-*N*-tosyl-2′-pyrrolyl)-4,5-dihydropyridazin-3-one 5c

Compound **5c** was synthesized according the procedure described for the synthesis of **5a** by refluxing a mixture of **4c**, hydrazine hydrate and acetic acid for 23 h. The crude product was purified by column chromatography to give **5c** (35%) as a colourless solid; mp 170–171 °C; ν_{max}/cm^{-1} 3224 (NH), 1678 (CO), 1365, 1341, 1173 and 1133; ^{1}H NMR (300 MHz, DMSO-d_6) 10.89 (1H, s), 7.60 (2H, d, *J*=8.2 Hz), 7.40 (2H, d, *J*=8.2 Hz), 6.37 (1H, d, *J*=3.2 Hz), 6.08 (1H, d, *J*=3.2 Hz), 2.75 (2H, t, *J*=7.9 Hz), 2.65 (2H, q, *J*=7.4 Hz), 2.43 (2H, t, *J*=7.9 Hz), 2.37 (3H, s) and 1.11 (3H, t, *J*=7.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) 167.3 (CO), 147.2, 145.3, 140.9, 134.8, 134.1 (all C), 130.1 (2×CH), 126.1 (2×CH), 116.5, 112.5 (both CH), 27.7, 26.5, 21.4 (all CH_2), 21.0 and 13.1 (both CH_3); *m*/*z* (ESI) 368 (M^++Na, 80%), 346 (M^++H, 100), 330 (10), 318 (18) and 302 (10) [found: M^++H, 346.1225. $C_{17}H_{20}N_3O_3S$ requires 346.1225].

4.7. 6-(*N*-Tosyl-2′-pyrrolyl)-pyridazin-3-one 6a

A mixture of dihydropyridazin-3-one **5a** (5.86 g, 18.5 mmol) and selenium dioxide (2.67 g, 24 mmol) in dioxane (200 mL) was heated to reflux for 22 h. After being allowed to cool to rt, the bulk of the solvent was evaporated in vacuo. The residue was partitioned between water (30 mL) and DCM (30 mL). The separated aqueous phase was extracted with DCM (4×10 mL). The combined organic extracts were dried (Na_2SO_4), filtrated and evaporated in vacuo. The

residue was purified by column chromatography on silica gel with DCM–EtOAc (5:1) as eluent to give *pyridazin-3-one* **6a** (3.93 g, 67%) as a yellow solid; mp 212–233 °C; ν_{max}/cm^{-1} 3146 (NH), 1685 (CO), 1596, 1368, 1170, 1149 and 1065; ^1H NMR (300 MHz, DMSO-d_6) 13.16 (1H, s), 7.69 (2H, d, J=8.1 Hz), 7.57 (1H, dd, J=3.3, 1.8 Hz), 7.53 (1H, d, J=9.6 Hz), 7.40 (2H, d, J=8.1 Hz), 6.89 (1H, d, J=9.6 Hz), 6.57 (1H, dd, J=3.3, 1.8 Hz), 6.43 (1H, t, J=3.3 Hz) and 2.38 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$), 160.6 (CO), 145.4, 139.9 (both C), 136.2 (CH), 135.6 (C), 129.9 (2×CH), 128.4 (CH), 127.0 (2×CH), 125.7, 118.0, 112.9 (all CH) and 21.7 (CH_3); *m*/*z* (ESI) 338 (M^++Na, 15%), 316 (M^++H, 100), 261 (15) and 217 (18) [found: M^++H, 316.0753. $C_{15}H_{14}N_3O_3S$ requires 316.0756].

4.8. 6-(5′-Phenyl-*N*-tosyl-2′-pyrrolyl)-pyridazin-3-one 6b

Compound **6b** was synthesized according to the procedure described for the synthesis of **6a** by refluxing a mixture of **5b** and selenium dioxide in dioxane for 22 h, in 66% isolated yield as an amorphous solid; ν_{max}/cm^{-1} 3264 (NH), 1680 (CO), 1604, 1570, 1404, 1162 and 1134; ^1H NMR (300 MHz, DMSO-d_6) 13.08 (1H, s), 12.44 (1H, m), 7.99 (1H, d, J=9.9 Hz), 7.51–7.41 (7H, m), 7.26 (2H, d, J=8.1 Hz), 7.20 (1H, d, J=2.7 Hz), 6.95 (1H, d, J=9.9 Hz) and 2.32 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) 160.1 (CO), 143.1, 140.5, 138.0, 136.8 (all C), 131.1, 130.0 (both CH), 129.9 (2×CH), 129.5 (2×CH), 128.7 (CH), 128.0 (C), 127.7 (2×CH), 126.3 (2×CH), 121.9 (C), 110.5 (CH) and 20.9 (CH_3); *m*/*z* (ESI) 414 (M^++Na, 100%) and 392 (M^++H, 100) [found: M^++H, 392.1068. $C_{21}H_{18}N_3O_3S$ requires 392.1069].

4.9. 6-(5′-Ethyl-*N*-tosyl-2′-pyrrolyl)-pyridazin-3-one 6c

Compound **6c** was synthesized according to the procedure described for the synthesis of **6a** by refluxing a mixture of **5c**, selenium dioxide in dioxane for 22 h, in 35% isolated yield as a brown solid; mp 164–166 °C; ν_{max}/cm^{-1} 1676 (CO), 1653, 1604, 1366 and 1175; ^1H NMR (300 MHz, DMSO-d_6) 13.13 (1H, s), 7.57–7.53 (3H, m), 7.40 (2H, d, J=8.1 Hz), 6.85 (1H, d, J=9.6 Hz), 6.47 (1H, d, J=3.6 Hz), 6.16 (1H, d, J=3.6 Hz), 2.71 (2H, q, J=7.2 Hz), 2.37 (3H, s) and 1.44 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) 160.1 (CO), 145.3, 140.7, 140.1 (all C), 136.3 (CH), 135.0, 132.0 (both C), 130.2 (2×CH), 127.5 (CH), 126.1 (2×CH), 117.2, 112.3 (both CH), 21.4 (CH_2), 21.0 and 13.1 (both CH_3); *m*/*z* (ESI) 366 (M^++Na, 100%), 344 (M^++H, 56), 330 (11), 318 (15) and 302 (11) [found: M^++Na, 366.0890. $C_{17}H_{17}N_3NaO_3S$ requires 366.0888].

4.10. 3-Chloro-6-(*N*-tosyl-2′-pyrrolyl)pyridazine 7a

A mixture of pyridazin-3-one **6a** (1.49 g, 4.7 mmol) and phosphorus oxychloride (25 mL) was heated to reflux for 2.5 h. The excess of $POCl_3$ was evaporated in vacuo. The residue was partitioned between water (50 mL) and ethyl acetate (20 mL). The separated aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (20% ethyl acetate in DCM) to give *chloropyridazine* **7a** (1.23 g, 78%) as a yellow solid; mp 138–140 °C; ν_{max}/cm^{-1} 1595, 1474, 1399, 1365, 1175, 1147 and 1085; ^1H NMR (300 MHz, $CDCl_3$) 7.75 (1H, d, J=8.9 Hz), 7.58 (2H, d, J=8.7 Hz), 7.52 (1H, d, J=8.9 Hz), 7.49 (1H, dd, J=3.4, 1.8 Hz), 7.24 (2H, d, J=8.7 Hz), 6.63 (1H, dd, J=3.4, 1.8 Hz), 6.39 (1H, t, J=3.4 Hz) and 2.38 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 155.7, 153.1, 145.4, 135.4 (all C), 130.8 (CH), 129.8 (2×CH), 127.3 (2×CH), 127.1, 126.6, 119.4, 113.3 (all CH) and 21.6 (CH_3); *m*/*z* (ESI) 356 (M^+ (^{35}Cl)+Na, 5%), 336 (M^+ (^{37}Cl)+H, 30) and 334 (M^+ (^{35}Cl)+H, 100) [found: M^++H, 334.0412. $C_{15}H_{13}{}^{35}ClN_3O_2S$ requires 334.0417].

4.11. 3-Bromo-6-(5′-phenyl-*N*-tosyl-2′-pyrrolyl)pyridazine 7b

Compound **7b** was synthesized according to the procedure described for the synthesis of **7a** by refluxing a mixture of **6b** and phosphorus oxybromide in toluene for 6.5 h, in 80% isolated yield as a yellow solid; mp 258–264 °C; ν_{max}/cm^{-1} 1587, 1470, 1402, 1302, 1169, 1161, 1146 and 1136; ^1H NMR (300 MHz, DMSO-d_6) 12.98 (1H, m), 8.21 (1H, d, J=9.0 Hz), 8.06 (1H, d, J=9.0 Hz), 7.58–7.43 (8H, m), 7.28 (2H, d, J=7.8 Hz) and 2.32 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) 151.6, 145.7, 143.2, 140.1, 137.9 (all C), 132.2 (CH), 129.9 (2×CH), 129.5 (2×CH), 129.4 (C), 129.0 (CH),127.7 (2×CH), 126.3 (2×CH), 125.9 (CH), 122.9 (C), 113.1 (CH) and 20.9 (CH_3); *m*/*z* (ESI) 478 (M^+ (^{81}Br)+Na, 95%), 476 (M^+ (^{79}Br)+Na, 93), 456 (M^+ (^{81}Br)+H, 100) and 454 (M^+ (^{79}Br)+H, 96) [found: M^++H, 454.0225. $C_{21}H_{17}BrN_3O_2S$ requires 454.0225].

4.12. 3-Bromo-6-(5′-ethyl-*N*-tosyl-2′-pyrrolyl)pyridazine 7c

Compound **7c** was synthesized according to the procedure described for the synthesis of **7a** by refluxing a mixture of **6c** and phosphorus oxybromide in toluene for 2 h, in 20% isolated yield as a brown oil; ν_{max}/cm^{-1} 1596, 1533, 1370 and 1173; ^1H NMR (300 MHz, $CDCl_3$) 7.56 (2H, s) 7.53 (2H, d, J=8.4 Hz), 7.17 (2H, d, J=8.4 Hz), 6.52 (1H, d, J=3.6 Hz), 6.03 (1H, dt, J=3.6, 0.9 Hz), 2.75 (2H, qd, J=7.5, 0.9 Hz), 2.30 (3H, s) and 1.16 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 154.8, 146.8, 145.2, 143.2, 134.9 (all C), 131.7, 130.0 (both CH), 129.9 (2×CH), 126.7 (2×CH), 119.7, 112.7 (both CH), 22.1 (CH_2), 21.6 and 13.0 (both CH_3); *m*/*z* (ESI) 430 (M^+ (^{81}Br)+Na, 55%), 428 (M^+ (^{79}Br)+Na, 49), 408 (M^+ (^{81}Br)+H, 100) and 406 (M^+ (^{79}Br)+H, 100) [found: M^++H, 406.0224. $C_{17}H_{17}{}^{79}BrN_3O_2S$ requires 406.0225].

General procedure for Suzuki cross-coupling reaction: A solution of chloropyridazine **7a**/**11** (0.24 mmol), arylboronic acid (0.32 mmol), tetrakis(triphenylphosphine) palladium (0.01 mmol) and potassium carbonate (0.64 mmol) in toluene (20 mL)/methanol (5 mL) was heated to reflux under nitrogen for 12 h (14.5 h in the case of compound **11**), then cooled, filtered and evaporated. The crude product was purified by column chromatography.

4.13. 3-Phenyl-6-(2′-pyrrolyl)pyridazine (8, Ar=Ph)

Yellow solid; mp 220–223 °C; ν_{max}/cm^{-1} 1595, 1474, 1399, 1365, 1175, 1147 and 1085; ^1H NMR (300 MHz, $CDCl_3$) 9.97 (1H, br s), 8.11–8.07 (2H, m), 7.82 (1H, d, J=9.0 Hz), 7.73 (1H, d, J=9.0 Hz), 7.57–7.48 (3H, m), 7.05 (1H, m), 6.81 (1H, m) and 6.36 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 156.4, 150.9, 136.3 (all C), 129.8 (CH), 129.0 (2×CH), 128.3 (C), 126.6 (2×CH), 124.3, 122.4, 121.7, 110.6 and 109.4 (all CH); *m*/*z* (ESI) 244 (M^++Na, 100%), 222 (M^++H, 95) and 195 (75) [found: M^++H, 222.1034. $C_{14}H_{12}N_3$ requires 222.1031].

4.14. 3-(4′-*tert*-Butylphenyl)-6-(2″-pyrrolyl)pyridazine (8, Ar=4-^{t}BuPh)

Yellow solid; mp 243–245 °C; ν_{max}/cm^{-1} 3270 (NH), 1594, 1564, 1457 and 1123; ^1H NMR (300 MHz, $CDCl_3$) 9.97 (1H, br s), 8.04 (2H, d, J=8.6 Hz), 7.81 (1H, d, J=9.0 Hz), 7.71 (1H, d, J=9.0 Hz), 7.55 (2H, d, J=8.6 Hz), 7.04 (1H, m), 6.79 (1H, m), 6.36 (1H, m) and 1.38 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 156.3, 153.2, 150.6, 133.3, 128.0 (all C), 126.3 (2×CH), 126.0 (2×CH), 124.3, 122.6, 122.2, 110.5, 109.6 (all CH) and 31.2 (3×CH_3); *m*/*z* (ESI) 300 (M^++Na, 26%) and 278 (M^++H, 100) [found: M^++H, 278.1657. $C_{18}H_{20}N_3$ requires 278.1657].

4.15. 3-(4′-Methoxyphenyl)-6-(2″-pyrrolyl)pyridazine (8, Ar =4-MeOPh)

Yellow solid; mp 225–227 °C; ν_{max}/cm^{-1} 3242 (NH), 1607, 1568, 1510, 1458, 1437, 1397, 1297, 1255, 1182, 1122 and 1034; ^1H NMR (300 MHz, $CDCl_3$) 9.91 (1H, br s), 8.05 (2H, d, J=9.0 Hz), 7.77 (1H, d, J=9.0 Hz), 7.69 (1H, d, J=9.0 Hz), 7.06–7.03 (3H, m), 6.79 (1H, m), 6.36 (1H, m) and 3.89 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 161.2, 156.0, 150.0, 128.5 (all C), 128.0 (2×CH), 127.7 (C), 124.1, 122.9, 122.3 (all CH), 114.5 (2×CH), 110.7, 109.9 (both CH) and 55.4 (CH_3); m/z (ESI) 274 (M^++Na, 14%) and 252 (M^++H, 100) [found: M^++H, 252.1137. $C_{15}H_{14}N_3O$ requires 252.1137].

4.16. 3-(3′-Nitrophenyl)-6-(2″-pyrrolyl)pyridazine (8, Ar=3-O_2NPh)

Yellow solid; mp 214–217 °C; ν_{max}/cm^{-1} 3267 (NH), 1525, 1454, 1443, 1417, 1348 and 1119; ^1H NMR (300 MHz, DMSO-d_6) 12.00 (1H, s), 8.99 (1H, s), 8.62 (1H, d, J=7.9 Hz), 8.37–8.34 (2H, m), 8.11 (1H, d, J=9.1 Hz), 7.86 (1H, t, J=7.9 Hz), 7.05 (2H, m) and 6.26 (1H, m); ^{13}C NMR (75 MHz, DMSO-d_6) 153.3, 152.1, 148.5, 137.8 (all C), 132.5, 130.6 (both CH), 127.7 (C), 124.9, 124.0, 122.8, 122.5, 120.6, 110.8 and 110.0 (all CH); m/z (ESI) 267 (M^++H, 40%), 239 (25) and 217 (100) [found: M^++H, 267.0884. $C_{14}H_{11}N_4O_2$ requires 267.0882].

4.17. 3-(2′-Methylphenyl)-6-(2″-pyrrolyl)pyridazine (8, Ar=2-MePh)

Yellow solid, mp 143–145 °C; ν_{max}/cm^{-1} 3259 (NH), 1592, 1563, 1462, 1422 and 1122; ^1H NMR (300 MHz, $CDCl_3$) 10.79 (1H, s), 7.74 (1H, d, J=8.9 Hz), 7.53–7.32 (5H, m), 7.05 (1H, m), 6.82 (1H, m), 6.33 (1H, m) and 2.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 159.0, 150.6, 137.2, 136.2 (all C), 131.0, 129.6, 129.0 (all CH), 127.9(C), 127.8, 126.1, 122.7, 122.0, 110.3, 109.7 (all CH) and 20.4 (CH_3); m/z (ESI) 258 (M^++Na, 12%) and 236 (M^++H, 100) [found: M^++H, 236.1187. $C_{15}H_{14}N_3$ requires 236.1188].

4.18. 3-(4′-Fluorophenyl)-6-(2″-pyrrolyl)pyridazine (8, Ar=4-FPh)

Yellow solid; mp 207–209 °C; ν_{max}/cm^{-1} 3276 (NH), 1602, 1458, 1234 and 1119; ^1H NMR (300 MHz, DMSO-d_6) 11.93 (1H, s), 8.25–8.21 (2H, m), 8.17 (1H, d, J=9.1 Hz), 8.03 (1H, d, J=9.1 Hz), 7.39 (2H, t, J=8.8 Hz), 7.00 (2H, d, J=8.8 Hz) and 6.23 (1H, m); ^{13}C NMR (75 MHz, DMSO-d_6) 163.1 (C, d, J_{FC} 245.3), 154.4, 151.5, 132.6 (all C), 128.5 (2×CH, d, J 8.5), 127.9 (C), 124.2 (CH), 122.4 (2×CH), 116.0, 115.7, 110.1 and 109.8 (all CH); m/z (ESI) 262 (M^++Na, 10%) and 240 (M^++H, 100) [found: M^++H, 240.0937. $C_{14}H_{11}FN_3$ requires 240.0937].

4.19. 3-Chloro-6-(2′-pyrrolyl)pyridazine 9[12]

Colourless solid; mp 174–175 °C (lit.[12] mp 182.4–182.7 °C); ^1H NMR (300 MHz, $CDCl_3$) 9.89 (1H. br s), 7.63 (1H, d, J=9.0 Hz), 7.41 (1H, d, J=9.0 Hz), 7.05 (1H, m), 6.77 (1H, m) and 6.34 (1H, m); m/z (ESI) 204 (M^+ (^{37}Cl)+Na, 86%), 202 (M^+ (^{35}Cl)+Na, 100), 182 (M^+ (^{37}Cl)+H, 12) and 180 (M^+ (^{35}Cl)+H, 33).

4.20. 3-Methoxy-6-(2′-pyrrolyl)pyridazine 10[12]

Colourless solid; mp 135–137 °C; ^1H NMR (300 MHz, $CDCl_3$) 9.76 (1H. br s), 7.62 (1H, d, J=9.3 Hz), 6.99–6.95 (2H, m), 6.66 (1H, m), 6.31 (1H, m) and 4.13 (3H, s).

4.21. 3-(*N*-Benzyl-2′-pyrrolyl)-6-chloropyridazine 11

To a suspension of NaH (29 mg, 1.2 mmol) in dry THF (10 mL), were added chloropyridazine **9** (178 mg, 1 mmol) and benzyl bromide (256 mg, 1.5 mmol). The resulting mixture was stirred at rt for 72 h. Water (2 mL) was added dropwise to quench the reaction. The bulk of THF was removed in vacuo. The residue was partitioned between water (15 mL) and DCM (10 mL). The separated aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts were dried (Na_2SO_4), filtrated and evaporated in vacuo. The residue was purified by column chromatography on silica gel with EtOAc–petroleum ether (1:5) as eluent to give *chloropyridazine* **11** (109 mg, 41%) as a yellow solid; mp 96–97 °C; ν_{max}/cm^{-1} 1574, 1540, 1472, 1438, 1427, 1394, 1332, 1157 and 1086; ^1H NMR (300 MHz, $CDCl_3$) 7.60 (1H, d, J=9.0 Hz), 7.35 (1H, d, J=9.0 Hz), 7.24–6.93 (5H, m), 6.94 (1H, dd, J=2.7, 1.8 Hz), 6.72 (1H, dd, J=3.9, 1.8 Hz), 6.28 (1H, dd, J=3.9, 2.7 Hz) and 5.81 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 153.6, 153.3, 138.6 (all C), 128.5 (CH), 128.4 (2×CH), 128.1 (CH), 127.4 (C), 127.2 (CH), 127.9 (2×CH), 126.8, 113.9, 109.2 (all CH) and 52.9 (CH_2); m/z (ESI) 294 (M^+ (^{37}Cl)+Na, 15%), 292 (M^+ (^{35}Cl)+Na, 55), 272 (M^+ (^{37}Cl)+H, 25) and 270 (M^+ (^{35}Cl)+H, 100) [found: M^++H, 270.0797. $C_{15}H_{13}ClN_3$ requires 270.0798].

4.22. 3-(*N*-Benzyl-2′-pyrrolyl)-6-phenylpyridazine 12

Yellow solid; mp 138–140 °C; ν_{max}/cm^{-1} 1587, 1551, 1472, 1453, 1402, 1082 and 1070; ^1H NMR (300 MHz, $CDCl_3$) 8.08–8.04 (2H, m), 7.77 (1H, d, J=9.0 Hz), 7.70 (1H, d, J=9.0 Hz), 7.52–7.49 (3H, m), 7.26–7.09 (5H, m), 6.91 (1H, dd, J=2.7, 1.8 Hz), 6.74 (1H, dd, J=3.9, 1.8 Hz), 6.31 (1H, dd, J=3.9, 2.7 Hz) and 5.95 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 155.9, 153.2, 138.8, 136.2 (all C), 129.7 (CH), 128.9 (2×CH), 128.6 (C), 128.4 (2×CH), 127.7, 127.1 (both CH), 127.0 (2×CH), 126.7 (2×CH), 125.1, 124.1, 113.2, 109.0 (all CH) and 52.7 (CH_2); m/z (ESI) 334 (M^++Na, 15%) and 312 (M^++H, 100) [found: M^++H, 312.1502. $C_{21}H_{18}N_3$ requires 312.1501].

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.05.055. These data include MOL files and InChIKeys of the most important compounds described in this article.

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