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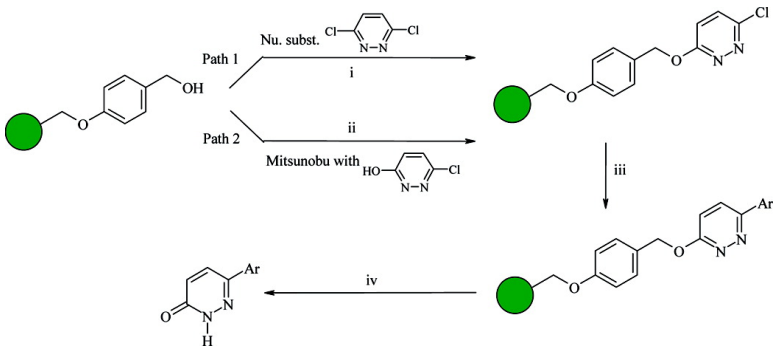

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Solid-Phase Syntheses of 6-Arylpyridazin-3(*2H*)-Ones

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The 3-chloropyridazine moiety was immobilized on a Wang resin, using two different methodologies. The first of these involved direct nucleophilic substitution of 3,6-dichloropyridazine with the alcoholate of Wang resin. The experimental conditions were optimized. The second method involved a Mitsunobu reaction between the Wang resin and 6-chloropyridazin-3-ol during which a problem of regioselectivity was observed. The so-obtained chloropyridazine-containing resins were subsequently reacted with various arylboronic acids under Suzuki conditions. Acid cleavage yielded 6-arylpyridazin-3(2*H*)-ones with high chemical purity.

Introduction

The arylpyridazinone moiety is found in many compounds of biological interest. For example, compounds that contain this motif have been used as antibacterial,[1] antidepressant,[2] hypotensive,[3−5] antianemic,[6] analgesic,[7,8] nephrotropic,[9−12] antiinflammatory,[2,7,8,13,14] cardiotonic,[3,15,16] anticancer,[13] antiaggregative,[17] pesticidal,[18] antifongic,[19] and herbicidal agents.[20]

Because of the wide range of biological activities of this class of compounds, we chose to develop solid-phase synthesis routes for the production of novel arylpyridazinone derivatives for our general screening collection.

Previously reported synthetic routes to arylpyridazinones include (i) functionalization of pyridazines, (ii) cross-coupling reactions, and (iii) construction of the pyridazine ring by condensation of dicarbonyl compounds with hydrazines. Some other pyridazine compounds have been synthesized by solid-phase synthesis.[21] However, to our knowledge, no solid-phase synthesis of the targeted arylpyridazinones compounds has been reported.

This paper describes our investigation of two solid-phase synthetic routes to arylpyridazinones.

In the first synthesis route, 3,6-dichloropyridazine was coupled to a Wang resin via nucleophilic substitution of one of its Cl atoms (Path 1). Suzuki cross-coupling reaction of an arylboronate with the attached chloropyridazine moiety resulted in the formation of an arylpyridazine, which afforded an arylpyridazinone after cleavage. Alternatively, the Wang resin was reacted with 3-chloropyridazin-6-ol under Mitsunobu conditions (Path 2) to afford the Wang resin bearing the chloropyridazine moiety (Scheme 1).

The methodology outlined in Scheme 1 has the following advantages. Both 3,6-dichloropyridazine and 3-chloropyridazin-6-ol are commercially available, as are a large number of aryl (and heteroaryl) boronates, thus permitting arylpyridazinones of great structural diversity to be obtained. Furthermore, the coupling of boronates bearing a reactive substituent allows a second reaction to be performed on the resin, resulting in facile access to arylpyridazinones of even greater structural diversity.

Results and Discussion

Nucleophilic substitution was first tested in solution with 3,6-dichloropyridazine and *para*-methoxybenzylic alcohol as a mimic for the Wang resin with sodium hydride (NaH) as a base (Scheme 2).

This nucleophilic substitution was then tested with the Wang resin and under various experimental conditions. (See Table 1.) Coupling yields were determined by elemental analyses (nitrogen and halogen).[22] The analysis of the IR spectra of the coupled resin allowed us to verify the absence or the decrease of the signal corresponding to ν(OH), ca. 3500 cm^{-1}.

Note: Long reaction times (6 days) were required to obtain a quantitative yield. To shorten the reaction time, some activation conditions were tested, including sonication and the use of crown ethers or a chelating agent (tris[2-(2-methoxyethoxy)-ethyl]amine, TDA_1). (See Table 2.)

All the activation methods tested were efficient to promote the nucleophilic substitution, which could be performed within a few hours instead of days without activation.

The best choice seems to be the use of TDA_1 with potassium *tert*-butoxide (*t*-BuOK) as a base (see entry 9 in Table 2).

Another way to graft a pyridazine on the Wang resin is to use the Mitsunobu reaction with 3-chloropyridazin-6-ol (Scheme 1, Path 2). Because it is well-known that 3-hydroxypyridazine exists predominantly in the oxo form,[23] it could be thought, at a first glance, that the Mitsunobu reaction

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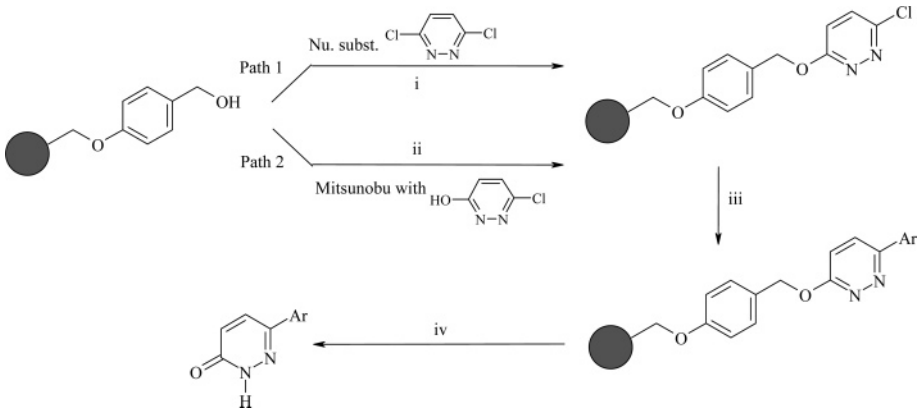
Scheme 1[a]



[a] Step iii, Suzuki cross coupling of arylboronates; step iv, cleavage of the resin.

Scheme 2

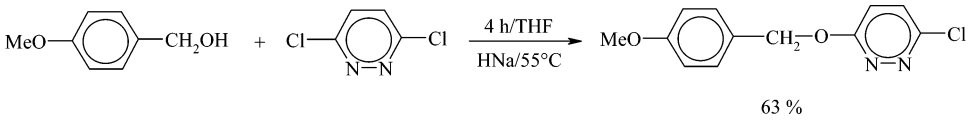


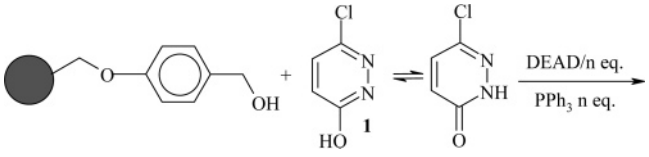
Table 1. Reaction Conditions for Coupling with Wang Resin

entry	base	solvent	θ (°C)	time (h)	coupling analysis	ν(OH), IR
1	*t*-BuOLi, 4 equiv	THF	65	144	98%	very small
2	NaH, 5 equiv	THF	85	142	100%	no
3	NaH, 5 equiv	DMF	85	48	96%	very small
4	*n*-BuLi, 3 equiv	THF	65	72	24%	strong
5	*n*-BuLi, 3 equiv	THF	65	142	89%	small

Table 2. Reaction Conditions for Coupling under Activation

entry	base	solvent	θ (°C)	time (h)	mode of activation	yield (%)	ν(OH), IR
1	NaH, 2 equiv	THF	20−44	10	))))	95	very small
2	NaH, 2 equiv	THF	20−44	5	))))	40	strong
3	*t*-BuOH, 1.5 equiv	DMF	80	84	18Cr6 (0.1)	100	no
4	*n*-BuLi, 1.5 equiv	THF	65	84	12Cr4 (1.5)	94	small
5	NaH, 2 equiv	DMF	80	84	15Cr5 (0.2)	100	very small
6	NaH, 2 equiv	DMF	80	24	15Cr5 (0.2)	100	very small
7	NaH, 2 equiv	DMF	80	13	15Cr5 (0.2)	99	small
8	*t*-BuOK, 1.5 equiv	THF	65	14	TDA_1	100	no
9	*t*-BuOK, 1.5 equiv	THF	65	5	TDA_1	100	no
10	*t*-BuOK, 1.5 equiv	THF	65	2.5	TDA_1	85	small

Scheme 3



is not suitable for our purpose. However, some *O*- or *N*-alkylation and *O*-glycosylation of pyridazin-3(*2H*)-ones have been reported in the literature.[24] Moreover, Chen and Munoz[25] have reported the successful grafting of pyridin-4-ol (which is known to exist in the oxo form) on Wang resin by this method. Various experimental conditions were tested (see Scheme 3 and Table 3).

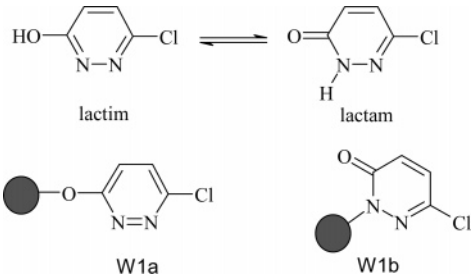
The yields were determined by elemental analyses of N and Cl atoms. With an excess of 8 equiv of **1** and 4 equiv of diethyl azodicarboxylate (DEAD) and PPh_3, the reaction was complete within 2 h (see entry 9 in Table 3). When the excess of DEAD was lowered, the reaction was not complete after 20 h (see entries 3 and 4 in Table 3). DEAD was replaced by diisopropyl azodicarboxylate (DIAD) (for practical reasons), which allowed us to obtain a quantitative yield within 5 h (instead of 2 h with DEAD (see entry 9 in Table 3)).

Table 3. Reaction Conditions for Coupling, According to the Mitsunobu Reaction

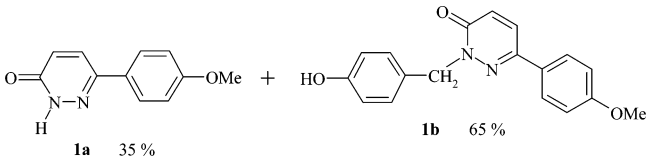
entry	**1** content (equiv)	DEAD content (equiv)	time (h)	yield (%)	ν(OH), IR
1	8	4	20	98	no
2	6	3	20	100	no
3	4	2	25	90	no
4	2	1	20	86	small
5	8	4	48	>95	no
6	8	4	15	>95	no
7	8	4	8	>95	no
8	8	4	4	>95	no
9	8	4	2	94	no
10	8	4	1		very small

Analyses indicated that the resin was completely coupled with pyridazine **1** but gave no information concerning the regioselectivity of this reaction. As discussed previously, two

Scheme 4



Scheme 5



coupling sites were possible on the heterocycle: the O atom of the lactim or the N atom of the lactam (Scheme 4).

To evaluate the chemoselectivity of the Mitsunobu reaction with the Wang resin, the coupled resin $\mathbf{W_{1(a+b)}}$ was first reacted with *p*-methoxyphenylboronic acid to substitute the reactive Cl atom on the pyridazine ring by a *para*-methoxyphenyl group, then the reaction product on the resin $\mathbf{W_{1(a+b)}}$ was cleaved with a solution of trifluoroacetic acid (TFA) in dichloromethane (DCM, 50%). Two products were obtained (Scheme 5).

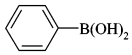
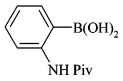
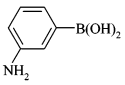
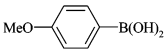
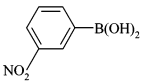
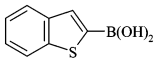
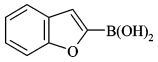
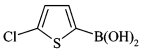
The *N*-adduct was qualitatively identified by the presence of an absorption signal between 1650 cm^{-1} and 1700 cm^{-1} in the IR spectra, which was attributed to the ν(C═O) of the lactam form.

Compound **1a** resulted from the cleavage of the pyridazine-*O*-linked resin but compound **1b** was obtained by the cleavage of the pyridazin-*N*-linked Wang resin. The proportions of **1a** and **1b** were 35/65.

However, in the pyridine series, Chen[22] reported only coupling via oxygen while a 4-pyridone form was also present. A Mitsunobu reaction was performed in the solution phase with *p*-methoxybenzylic alcohol and 3-chloro-6-hydroxypyridazine (**1**). Two products were obtained and separated; the proportions were 40% *O*-alkylated compounds and 60% *N*-alkylated compounds. These proportions were similar to those observed with the Wang resin (35/65).

The Mitsunobu approach for coupling hydroxydiazine on a Wang resin was efficient (quantitative yields) and fast (requiring less than 1 day) but is not suitable for compounds that have a strong lactam tautomerism. In this case, a mixture of *N*- and *O*-coupled products was obtained.

Table 4. Suzuki Reactions with Wang−Pyridazine Resin

entry	boronic acid	time (h)	N° of Wang resin	yield by analysis of ( )
1		72	$\mathbf{W_2}$	–
2		80	$\mathbf{W_3}$	85 % (N)
3		110	$\mathbf{W_4}$	91 % (N)
4		96	$\mathbf{W_5}$	–
5		105	$\mathbf{W_6}$	97 % (N)
6		96	$\mathbf{W_7}$	94 % (S)
7		98	$\mathbf{W_8}$	–
8		118	$\mathbf{W_9}$	98 % (S)

Coupling of the Second Cyclic Moiety

The pyridazine ring attached to the Wang resin has an halogen atom, which allows further cross coupling reactions to be performed.

Cross-coupling reactions on supported products[26] have been described for organoboron compounds,[27,28] tin derivatives,[29] and zinc derivatives.[30] The Suzuki reaction has been widely used in solid-phase synthesis. This reaction was first performed with resin $\mathbf{W_1}$ and some boronic acids (see Scheme 6 and Table 4).

The three resins—$\mathbf{W_2}$, $\mathbf{W_5}$, and $\mathbf{W_8}$—did not contain more nitrogen or sulfur than $\mathbf{W_1}$; therefore, their analyses could not be used to calculate yield.

All the Wang resins obtained ($\mathbf{W_2}$−$\mathbf{W_9}$) were cleaved to afford the aryl pyridazinones. This cleavage was performed with a solution of TFA in DCM. No subsequent treatment was performed; thus, a mixture of the free base and the trifluoroacetic salt was obtained and analyzed by liquid chromatography/mass spectroscopy (LC/MS) (see Table 5).

A larger-than-usual quantity of $\mathbf{W_1}$ was used for the coupling with phenyl boronic acid; the $\mathbf{W_2}$ resin was then

Scheme 6. Reactions Conditions for Suzuki Coupling on Wang Pyridazine Resin

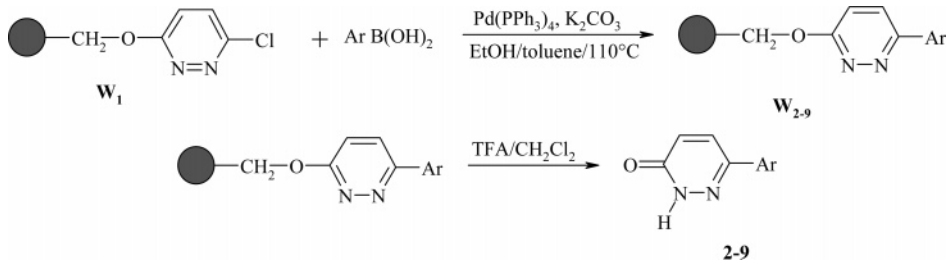


Table 5. Cleavage of Resins $\mathbf{W_3}-\mathbf{W_9}$[a]

entry	Wang resin	HPLC purity (%)	product	free base content (%)	trifluoroacetic salt content (%)
1	$\mathbf{W_3}$	38	**3**		
2	$\mathbf{W_4}$	96	**4**	43	53
3	$\mathbf{W_5}$	88	**5**	50	38
4	$\mathbf{W_6}$	57	**6**		
5	$\mathbf{W_7}$	85	**7**	64	21
6	$\mathbf{W_8}$	88	**8**	56	32
7	$\mathbf{W_9}$	88	**9**	48	40

[a] Note: Products **3** and **6**, coming from Wang resins $\mathbf{W_3}$ and $\mathbf{W_6}$, were obtained with lower purities. In the case of compound **3**, this may be explained by hydrolysis of the pivaloylamino group.

cleaved, and the substantial amount of product **2** that was obtained allowed us to isolate it, using the usual purification techniques. The overall yield was 59% starting from Wang resin. The other products were analyzed by the LC/MS method.

The introduction of a second heterocycle on the Wang resin by use of Suzuki reaction was successful with various boronic acids. The final cleavage reaction was also easy and gave good yields of biheteroaryl compounds.

Conclusion

The solid-phase synthesis of 6-aryl-pyridazin-3(*2H*)-ones was effective, using first, a nucleophilic substitution to graft the pyridazine ring to the Wang resin, then a Suzuki cross-coupling reaction, and finally a cleavage with TFA. Seven aryl pyridazinones were obtained. This procedure could easily be adapted for the production of a large library of biheteroaryl compounds. We have also shown that the Mitsunobu reaction is not suitable for the synthesis of $\mathbf{W_{1a}}$-type resin when compounds to be grafted have a strong lactam tautomerism. In this case, a mixture of *N*- and *O*-coupled products was obtained. However, because this reaction is fast and easy to perform, it could be used for the grafting of other heterocyclic compounds.

Experimental Procedures

Coupling by Nucleophilic Substitution in Solution. A solution of benzyl alcohol in the chosen solvent was degassed for 15 min with a stream of argon or nitrogen. The required amount of sodium hydride (NaH) was washed twice with pentane and suspended in the solvent (V mL). This suspension of NaH was added to benzyl alcohol dissolved in the solvent (V' mL), and the reaction mixture was stirred at 60 °C for 1 or 2 h, to obtain the sodium benzylate. A solution of the halogenated azine in the solvent (V'' mL) then was added, and the reaction was performed during time t at temperature T under a nitrogen or argon atmosphere with stirring. After cooling, the mixture was hydrolyzed with a saturated sodium hydrogenocarbonate solution (15 mL). The organic solvent was evaporated under vacuum, and the remaining aqueous solution was extracted with ethyl acetate (3 × 20 mL). The solution was dried over magnesium sulfate ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on a silica gel.

Coupling by Nucleophilic Substitution with Wang Resin. The experimental process was identical to the reaction in solution, except that benzyl alcohol was replaced by Wang resin. This resin was first washed with the reaction solvent and the magnetic stirring was replaced by an oscillating agitator; furthermore, NaH was used without washing. The final treatment of the reaction was the washing of the resin with tetrahydrofuran (THF), water/THF (1/1), methanol, THF, diethyl ether, toluene, and finally methanol. The washed resin was dried at 55 °C under vacuum for 24−36 h, and, for 1 g of resin, 50 mL of each solvent was used.

Coupling of Wang Resin under Mitsunobu Conditions. The Wang resin was placed in a round-bottomed flask and degassed during 0.5 h with a stream of nitrogen or argon. The resin was washed and swelled with THF (V mL) under inert gas. In three other flasks, the following solutions were prepared:

(1) Solution of the hydroxylated azine in dimethylformamide (DMF) (V' mL)

(2) Solution of triphenylphosphine in THF (V'' mL)

(3) Solution of diethyl azodicarboxylate (DEAD) in THF (V''' mL)

The first two solutions were successively introduced into the flask containing the Wang resin in THF (V mL), under oscillating agitation; the solution of DEAD (V''' mL) then was added dropwise at 0 °C. After warming to room temperature, the reaction was performed for a time period t (in hours). Thereafter, the resin was filtered, washed, and dried under vacuum, as noted previously.

Suzuki Cross Coupling in Solution. The halogenated product, toluene (V mL), ethanol (V' mL), a 2 M solution of potassium carbonate (V'' mL), and the boronic acid were introduced into a round-bottomed flask. The reaction mixture was degassed for 0.5 h and then placed under an inert atmosphere (nitrogen gas or argon). The catalyst—tetrakis triphenylphosphine palladium (1 to 10 mol %)—was added, and the mixture was warmed to a temperature T for a time period t (in hours). After cooling, water (10 mL) was added. The aqueous layer was extracted with DCM (3 × 40 mL). The organic layers were mixed, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified using silica gel chromatography.

Suzuki Cross Coupling with Wang Resin. The experimental procedure was the same as that described in solution. At the end of the reaction, the resin was washed and dried as noted previously.

Cleavage of the Resin-Bound Heterocycles. Wang resin was cleaved with a trifluoroacetic acid (20%) solution in DCM for a time period t (in minutes) at room temperature under oscillating agitation. The suspension was filtered, and the resin washed with DCM (3 × 50 mL). The combined filtrates were evaporated with a Gene Vac evaporator. LC/MS analysis was then performed, to determine the purity of the product and the proportions of the free base and the trifluoroacetate salt.

3-Chloro-6-[(*p*-methoxybenzyl)oxy]pyridazine. This product was first described by Tamura and Jojina in 1963.[31] Synthesis by nucleophilic substitution (procedure 1) of 3,6-dichloropyridazine (2.15 g, 14.43 mmol) with 4-methoxybenzyl alcohol (1.5 mL, 12.03 mmol); base: NaH (1.38 g, 36.1 mmol), $V_{THF} = 15$ mL, $V'_{THF} = 15$ mL, $V''_{THF} = 20$ mL;

time $t = 4$ h; temperature $T = 55$ °C. Product was obtained as a white powder (1.88 g, 63%), mp 111−113 °C after silica gel chromatography with petroleum ether and ethyl acetate as eluent (90/10). IR (KBr): ν 3054, 3016, 2964, 2924, 2841, 1618, 1586, 1518, 1440, 1415, 1318, 1250, 1147, 1029, 1003, 853, 816, 696 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.79 (s, 3H, OCH_3), 5.44 (s, 2H, $-OCH_2-$), 6.88−6.97 (m, 3H, $H_{pyr5} + H_{ph3}$), 7.34 (d, $J = 9.8$ Hz, 1H, H_{pyr4}), 7.40 (d, $J = 8.3$ Hz, 2H, H_{ph2}). ^{13}C NMR ($CDCl_3$): δ 55.2 (OCH_3), 69.3 ($-OCH_2-$), 113.9 (C_{Ph3}), 120.3 (C_{pyr5}), 127.9 (C_{ph1}), 130.4 (C_{ph2} or C_{ph4}), 130.8 (C_{pyr4} or C_{ph2}), 151.0 (C_{pyr3}), 159.7 (C_{ph4}), 164.1 (C_{pyr6}). Anal. Calcd for $C_{12}H_{11}N_2O_2Cl$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.29; H, 4.34; N, 11.09.

3-Chloropyridazine Coupled on Wang Resin (W_1). (a) Synthesis by nucleophilic substitution (procedure 2) (see entry 3 in Table 1) of 3,6-dichloropyridazine (0.93 g, 6.24 mmol) with Wang resin (2.08 g, L = 0.6 mmol/g); base: NaH (0.24 g, 6.24 mmol); $V_{DMF} = 20$ mL, $V'_{DMF} = 20$ mL, $V''_{DMF} = 20$ mL; time $t = 142$ h; temperature $T = 85$ °C. IR: complete disappearance of ν(OH). Anal. Calcd: N, 1.57; Cl, 2.00. Found: N, 1.47; Cl, 2.26. Coupling rate = 94% following nitrogen analysis, more than 100% following chlorine analysis.

(b) Synthesis by the Mitsunobu reaction $\mathbf{W_{1a}} + \mathbf{W_{1b}}$ (procedure 3) (see entry 7 in Table 3) of 6-chloropyridazin-3(*2H*)-one (1.00 g, 7.67 mmol) in DMF (10 mL) with Wang resin (1.08 g, L = 0.89 mmol/g) in THF (20 mL), PPh_3 (1.01 g, 3.84 mmol) in THF (15 mL) and DEAD (0.67 g, 3.84 mmol) in THF (10 mL); time $t = 8$ h; room temperature. IR: complete disappearance of ν(OH). Anal. Calcd: N, 2.27; Cl, 2.87. Found: N, 2.28; Cl, 2.86. Coupling rate ≈ 100% following the two analyses. Using this method, two products were obtained: $\mathbf{W_{1a}}$ and $\mathbf{W_{1b}}$, as mentioned in the first part.

3-Phenylpyridazine Coupled on Wang Resin (W_2). $\mathbf{W_2}$ resin was obtained via the Suzuki cross-coupling of $\mathbf{W_1}$ resin (1.43 g, L = 0.76 mmol/g) with phenyl boronic acid (0.23 g, 1.9 mmol), following the Suzuki reaction described in procedures 4 and 5. The volumes were $V_{tol} = 35$ mL, $V'_{EtOH} = 2.5$ mL, $V'' = 1.19$ mL; $Pd(PPh_3)_4$ (0.069 g, 0.059 mol) was added, and the reaction time was 72 h at a temperature of 110 °C.

6-Phenylpyridazine-3(2*H*)-one (2).[32] Cleavage following procedure 6 during $t = 15$ min. **2** was obtained as a white solid. mp = 119−201 °C. ^1H NMR ($CDCl_3$): δ 7.10 (d, $J = 9.9$ Hz, 1H, H_{pyr4}), 7.49−7.51 (m, 3H, $H_{ph3} + H_{ph4}$), 7.80 (d, $J = 9.9$ Hz, 1H H_{pyr5}), 7.82 (dd, $J = 7.5$ and 2 Hz, 2H, H_{ph2}), 11.50 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 126.4 (C_{ph2}), 129.4 (C_{ph3}), 130.0 (C_{ph4}), 130.7 (C_{pyr4}), 132.0 (C_{pyr5}), 134.9 (C_{ph1}), 146.0 (C_{pyr6}), 162.2 (C=O). Anal. Calcd for $C_{10}H_8NO_2$: C, 69.78; H, 4.68; N, 16.27. Found: C, 69.67; H, 4.53; N, 16.78.

3-(2-Pivaloylaminophenyl)pyridazine Coupled on Wang Resin (W_3). $\mathbf{W_3}$ resin was obtained via the Suzuki cross coupling (procedures 4 and 5) of $\mathbf{W_1}$ resin (1.32 g, L = 0.81 mmol/g) with 2-pivaloylaminophenylboronic acid (0.52 g, 2.75 mmol). $V_{tol} = 20$ mL; $V'_{EtOH} = 2$ mL, $V'' = 1.2$ mL; $Pd(PPh_3)_4$ (0.068 g, 0.059 mmol); time $t = 80$ h; 110 °C. IR: ν(CO) = 1686 cm^{-1}. Anal. Calcd: N, 3.05. Found: N, 2.93. Cross-coupling rate ≈ 85%.

6-(2-Pivaloylaminophenyl)pyridazin-3-(2*H*)-one (3). Cleavage following procedure 6 for 1 h. The residue (0.131 g) was analyzed and purified by LC/MS; it contained **3** (38%) and a compound that came from the cleavage of the pivaloyl group (57%). After further purification, **3** was obtained as a tan solid (0.024 g); mass spectrum (ESI): *m*/*z* 272 ($M + H^+$). ^1H NMR (CD_3OD): δ 1.28 (s, 9H, CH_3), 7.14 (d, $J = 9.9$ Hz, 1H, H_{pyr4}), 7.34 (t.d., $J = 7.7$ and 1.1 Hz, 1H, H_{ph4} or H_{ph5}), 7.50 (td, $J = 8$ Hz and 1.5 Hz, 1H, H_{ph5} or H_{ph4}), 7.67 (dd, $J = 7.7$ and 1.3 Hz, 1H, H_{ph3} or H_{ph6}), 7.89 (d, $J = 9.9$ Hz, 1H, H_{pyr5}), 8.03 (dd, $J = 8$ Hz and 1.3 Hz, 1H, H_{ph6} or H_{ph3}).

3-(3-Aminophenyl)pyridazine Coupled on Wang Resin (W_4). $\mathbf{W_4}$ resin was obtained via the Suzuki cross coupling (procedures 4 and 5) of $\mathbf{W_1}$ resin (1.24 g, L = 0.81 mmol/g) with 3-aminophenylboronic acid (0.34 g, 2.21 mmol); $V_{tol} = 20$ mL, $V'_{EtOH} = 2$ mL, $V'' = 1.1$ mL. $Pd(PPh_3)_4$ (0.064 g, 0.055 mmol); time $t = 110$ h; temperature $T = 110$ °C. IR $\nu(NH_2) = 3370$ cm^{-1}. Anal. Calcd: N, 3.25. Found: N, 3.16. Cross-coupling rate ≈ 91%.

6-(3-Aminophenyl)pyridazin-3(2*H*)-one (4).[33] Cleavage following procedure 6 during 15 min. The obtained residue (0.039 g) was analyzed by LC/MS and contained **4** in 96% purity, as a mixture of neutral product (43%) and trifluoroacetate salt (53%), tan solid; mass spectrum (ESI): *m*/*z* 188 $(M + H)^+$.

3-(4-Methoxyphenyl)pyridazine Coupled on Wang Resin (W_5). $\mathbf{W_5}$ resin was obtained via the Suzuki cross coupling (procedures 4 and 5) of $\mathbf{W_1}$ resin (0.97 g, L = 0.81 mmol/g) with 4-methoxyphenyl boronic acid (0.26 g, 1.72 mmol). $V_{tol} = 20$ mL, $V'_{EtOH} = 2$ mL, $V'' = 0.86$ mL. $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol); time $t = 96$ h; temperature $T = 110$ °C. Anal. Calcd: N, 2.14. Found: N, 1.97. These data could not indicate the achievement of the cross-coupling reaction.

6-(4-Methoxyphenyl)pyrazin-3(2*H*)one (5).[34] Cleavage of $\mathbf{W_5}$ resin following procedure 6 for 1 h. LC/MS analysis of the tan product indicated a 88% purity of product **5**, as a mixture of 50% free base and 38% trifluoroacetate salt.

3-(3-Nitrophenyl)pyridazine Coupled on Wang Resin (W_6). $\mathbf{W_6}$ resin was obtained via the Suzuki cross-coupling (procedure 5) of $\mathbf{W_1}$ resin (1.31 g, L = 0.81 mmol/g) with 3-nitrophenylboronic acid (0.39 g, 2.32 mmol). $V_{tol} = 20$ mL, $V'_{EtOH} = 2$ mL, $V'' = 1.17$ mL. $Pd(PPh_3)_4$ (0.067 g, 0.058 mmol); time $t = 105$ h; temperature $T = 110$ °C. Anal. Calcd: N, 3.18. Found: N, 3.15. Cross-coupling rate ≈ 97%.

6-(3-Nitrophenyl)pyridazine-3(2*H*)-one (6). Cleavage of $\mathbf{W_6}$ resin following procedure 6 during 75 min. LC/MS analysis of the residue (0.098 g) indicated a 57% purity, but the insolubility of the product in various solvents precluded the determination of the respective percentages of the free base and the trifluoroacetate salt; mass spectrum (ESI): *m*/*z* 218 ($M + H^+$).

3-(Benzo[*b*]thien-2-yl)pyridazine Coupled on Wang Resin (W_7). $\mathbf{W_7}$ resin was obtained via the Suzuki cross coupling (procedure 5) of $\mathbf{W_1}$ resin (1.01 g, L = 0.81 mmol/g) with 2-benzo[*b*]thienyl boronic acid (0.32 g, 1.8 mmol); $V_{tol} = 20$ mL; $V'_{EtOH} = 2$ mL; $V'' = 0.9$ mL. $Pd(PPh_3)_4$ (0.052 g, 0.045 mmol); time $t = 96$ h; temperature $T = 110$ °C. Anal. Calcd: N, 2.10; S, 2.40. Found: N, 2.09; S, 2.26.

Cross-coupling rate calculated with sulfur analysis ≈ 94%. Nitrogen analysis was not usable, because the change between $\mathbf{W_3}$ and $\mathbf{W_{15}}$ (2.27 and 2.10) was too low.

6-(Benzo[*b*]thien-2-yl)pyridazin-3(2*H*)-one (7). Cleavage of $\mathbf{W_7}$ following procedure 6 for 30 min. The LC/MS analysis of the residue (0.058 g) indicated a 85% purity, with 64% the free base and 21% the trifluoroacetate salt. Mass spectrum (ESI): *m*/*z* 229 $(M + H)^+$.

3-(Benzo[*b*]furan-2-yl)pyridazine Coupled on Wang Resin ($\mathbf{W_8}$). $\mathbf{W_8}$ resin was obtained via the Suzuki cross coupling (procedure 6) of $\mathbf{W_1}$ resin (0.97 g, L = 0.81 mmol/g) with 2-benzo[*b*]furylboronic acid (0.28 g, 1.72 mmol); V_{tol} = 20 mL; V'_{EtOH} = 2 mL; V'' = 0.86 mL. $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol); time t = 98 h; temperature T = 110 °C. Anal. Calcd: N, 2.13. Found: N, 2.18 (for $\mathbf{W_3}$: N, 2.27). The cross-coupling rate could not be calculated, because the nitrogen analyses of $\mathbf{W_3}$ and $\mathbf{W_{16}}$ were too similar.

6-(Benzo[*b*]furan-2-yl)pyridazin-3(2*H*)-one (8). Cleavage of $\mathbf{W_8}$ following procedure 6 for 35 min. The LC/MS analysis of the residue indicated a 88% purity for **8**, with 56% the free base and 21% the trifluoroacetate salt. Mass spectrum (ESI): *m*/*z* 213 $(M + H)^+$.

3-(5-Chlorothien-2-yl)pyridazine Coupled on Wang Resin ($\mathbf{W_9}$). $\mathbf{W_9}$ resin was obtained via the Suzuki cross coupling (procedure 5) of $\mathbf{W_1}$ resin (1.01 g, L = 0.81 mmol/g); V_{tol} = 20 mL, V'_{EtOH} = 2 mL, V'' = 0.86 mL. $Pd(PPh_3)_4$ (0.052 g, 0.045 mmol); time t = 118 h; temperature T = 110 °C. Anal. Calcd: S, 2.43. Found: S, 2.38. Cross-coupling rate = 98%. The analyses of chlorine and nitrogen could not be used, because the change between $\mathbf{W_1}$ and $\mathbf{W_9}$ was too small.

6-(5-chlorothien-2-yl)pyridazine-3(2*H*)-one (9).[35] Cleavage of $\mathbf{W_9}$ resin following procedure 6 for 15 min. The LC/MS analysis of the residue (0.076 g) indicated a 88% purity for **9**, with 48% the free base and 40% the trifluoroacetate salt. Mass spectrum (ESI): *m*/*z* 213 $(M + H)^+$. ^1H NMR (CD_3OD): δ 7.03 (d, J = 4 Hz, 1H, H_{thio}), 7.05 (d, J = 9.9 Hz, 1H, H_{pyr4}), 7.44 (d, J = 4 Hz, 1H, H_{thio}), 7.98 (d, J = 9.9 Hz, 1H, H_{pyr5}).

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