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Efficient one-step synthesis of 3-amino-6-arylpyridazines

Sébastien Guery, Isabelle Parrot, Yveline Rival* and Camille G. Wermuth

Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081 CNRS/ULP, Université Louis Pasteur, Faculté de Pharmacie, 74 route du Rhin, 67401 Illkirch Cedex, France

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Abstract—Starting from the commercially available 3-amino-6-chloropyridazine, 3-amino-6-arylpyridazines were prepared in good yields by means of a Suzuki cross-coupling reaction avoiding the somewhat lengthy four-step classic synthesis.

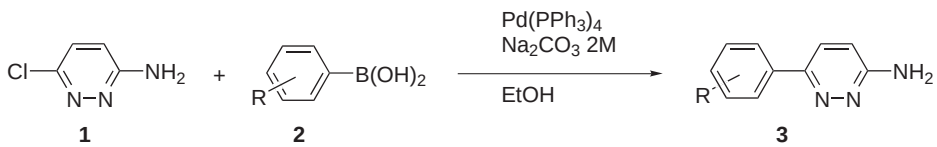
The pyridazine ring has demonstrated many synthetic[1] and several biological uses.[2] Despite the useful nature of pyridazines, there are a limited number of synthetic approaches to substitution on these electron deficient rings, and functionalization of the pyridazine nucleus continues to be of synthetic interest.[3–5]

More particularly there is still a need for efficient syntheses of 3-aminopyridazines. Effectively, among the methods described in the literature for the preparation of 3-amino-6-aryl pyridazines,[6–14] ammonolysis of the corresponding 6-aryl-3-halopyridazines[6] proceeds with extremely variable yields[6–8] despite vigorous experimental conditions (autoclave, 100–200°C, copper catalysts).

Attempts to replace the halogen atom by other leaving groups were also studied. Thus, 3-methylthio or 3-ethylthio derivatives have been reacted with ammonia to lead to the corresponding 3-aminopyridazines.[8] Yanai et al. have reported the even more difficult nucleophilic displacement of 3-alkoxyderivatives.[9] Starting from 3-mesylated and 3-tosylated pyridazines, Gregory et al. have demonstrated that the reaction with ammonia gave compounds with similar yields to that observed with 3-halopyridazines.[8,14]

Reagents other than ammonia were also examined. Atkinson et al.[10] have reported that the nucleophilic displacement of the halogen by urea, followed by alkaline hydrolysis leads to the expected compound with a 80% yield. Furthermore, Kappe et al.[11] have substituted the chlorine atom with sodium azide leading to a tetrazolo[1,5-*b*]pyridazine, which was then transformed into the corresponding amine via a Staudinger reaction. The use of potassium thiocyanide in EtOH, followed by hydrolysis of the intermediate thiourethane was also described. But, the most current method is the substitution of the halogen by hydrazine followed by the hydrogenolysis of the initially formed 3-hydrazinopyridazine.[12] The overall yields for this synthetic pathway previously described were found in the 35–45% range. The synthesis of 3-amino-6-arylpyridazines is possible in four steps, but is somewhat lengthy.[6–14]

In this paper, we describe a convenient approach to 3-amino-6-arylpyridazines from commercially available 3-amino-6-chloropyridazine by a Suzuki cross-coupling reaction (Scheme 1) (Table 1).[15] Such a reaction[3,16] was firstly applied to 3-chloro-6-methoxypyridazine and to 3-aminoalkyl-6-arylpyridazines.[16] This one-step reac-



Scheme 1.

Keywords: 3-amino-6-arylpyridazines; 3-amino-6-chloropyridazine; Suzuki cross-coupling; palladium(0) catalysis.
* Corresponding author. Tel.: +33 390 24 42 26; fax: +33 388 67 47 94; e-mail: rival@pharma.u-strasbg.fr

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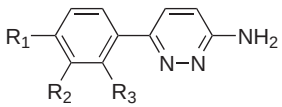
Table 1. Synthesis of 3-amino-6-arylpyridazines (**3a**–**3k**)



Compounds	R_1	R_2	R_3	Yield (%)
3a	H	H	H	50
3b	-O-CH_2-O-		″	40
3c	-OCH_3	H	″	45
3d	H	-OCH_3	″	45
3e	″	H	-OCH_3	45
3f	-Cl	″	H	40
3g	H	-Cl	″	50
3h	″	H	-Cl	35
3i	-CH_3	″	H	55
3j	H	-CH_3	″	60
3k	″	H	-CH_3	60

tion was used here for the first time with a pyridazine bearing a primary amine, without any protection, in order to obtain various substituted 3-amino-6-arylpyridazines with yields ranging from 35 to 60%. We observed that the use of phenylboronic acid bearing methyl groups provided the best yields, probably due to the electrodonor effect of the methyl substituent. Surprisingly, the same cross-coupling reaction with a methyl or a methoxy group in the *ortho* position on the phenylboronic acid does not require the replacement of Na_2CO_3 by $Ba(OH)_2$, a base conventionally used when a sterically hindered boronic acid is involved in a palladium cross coupling reaction.[17] The use of another type of catalyst ($Pd_2dba_3/PtBu_3$)[18] was also explored but the yields were not higher than those obtained with the conventional $Pd(PPh_3)_4$ catalyst.

In summary, starting from commercially available 3-amino-6-chloropyridazine, we have demonstrated that 3-amino-6-phenylpyridazines can be efficiently prepared in a one-step cross-coupling reaction. The advantages of this alternative approach reside in increased yields, easier operating conditions, mild conditions and a clearly shorter synthetic sequence.

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15. **General procedure for cross-coupling reactions**: A suspension of 3-amino-6-chloropyridazine (3.46 mmol, 1 equiv.) (**1**), arylboronic acid (3.98, 1.15 equiv.) (**2**), sodium carbonate 2 M (3.7 mL, 7.34 mmol, 2.12 equiv.) in toluene (20 mL) and EtOH (1.9 mL) was stirred under an atmosphere of argon for 30 min. $Pd(PPh_3)_4$ (0.14 mmol, 0.045 equiv.) was then added and the mixture was heated at 110°C for 32 h. The toluene was removed in vacuo, the residue diluted with H_2O and extracted with EtOAc (3×5 mL). The organic layers were dried over sodium sulfate, concentrated in vacuo and then purified by flash chromatography (AcOEt–MeOH 9:1, TEA 2%). Satisfactory spectral data were obtained for all new compounds (**3a**–**3k**): 3-Amino-6-phenylpyridazine (**3a**): white needles; mp 140°C; R_f 0.40 (AcOEt–MeOH 9:1) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.89 (m, 2H); 6.84 (d, J=9.5 Hz, 1H); 7.39–7.95 (m, 5H); 7.97 (d, J=9 Hz, 1H). 3-Amino-6-(3,4-methylenedioxy phenyl) pyridazine (**3b**): yellow needles; mp 166°C; R_f 0.55 (AcOEt–MeOH 9:1/TEA 2%) ^{1}H NMR (CD_3OD, 300 MHz) δ 4.75 (m, 2H); 6.04 (s, 2H); 6.94 (d, J=8 Hz, 1H); 7.15 (d, J=9 Hz, 1H); 7.39 (d, J=6.5 Hz, 1H); 7.46 (s, 1H); 7.75 (d, J=9 Hz, 1H). 3 - Amino - 6 - (4 - methoxyphenyl)pyridazine (**3c**): white needles; mp 195°C; R_f 0.16 (AcOEt–MeOH 9:1/TEA 2%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 3H); 4.75 (m, 2H); 6.81 (d, J=9 Hz, 1H); 7.00 (d, J=6.5 Hz, 2H); 7.58 (d, J=9 Hz, 1H); 7.91 (d, J=6.5 Hz, 2H). 3-Amino-6-(3-methoxyphenyl)pyridazine (**3d**): white needles; mp 124°C; R_f 0.19 (AcOEt–MeOH 9:1/TEA 2%) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.83 (s, 3H); 4.51 (m, 2H); 6.83 (d, J=9 Hz, 1H); 7.24 (d, J=8 Hz, 1H); 7.37 (t, J=7.5 Hz, 1H); 7.64 (d, J=9 Hz, 1H); 7.72 (d, J=8.0 Hz, 1H); 7.83 (s, 1H). 3 - Amino - 6 - (2 - methoxyphenyl)pyridazine (**3e**): white needles; mp 135°C; R_f 0.17 (AcOEt–MeOH 9:1/TEA 2%) ^{1}H NMR ($CDCl_3$, 300 MHz): 3.83 (s, 3H); 5.14 (m, 2H); 6.76 (d, J=9.0 Hz, 1H); 6.98 (d, J=8.5 Hz, 1H); 7.06 (t, J=7.5 Hz, 1H); 7.37 (t, J=8 Hz, 1H); 7.71 (d, J=9 Hz, 1H); 7.81 (d, J=8 Hz, 1H). 3-Amino-6-(4-chlorophenyl)-pyridazine (**3f**): white needles; mp 155°C; R_f 0.20 (AcOEt–MeOH 9:1/TEA 2%) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.87 (m, 2H); 6.84 (d, J=9.0 Hz, 1H); 7.44 (d, J=7 Hz, 2H); 7.61 (d, J=10 Hz, 1H); 7.90 (d, J=7.0 Hz, 2H). 3-Amino-6-(3-chlorophenyl)pyridazine (**3g**): yellow needles; mp 153°C; R_f 0.53 (AcOEt–MeOH 9:1/TEA 2%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.87 (m, 2H); 6.84 (d, J=9.0 Hz, 1H); 7.39–7.41 (m, 2H); 7.61 (d, J=9 Hz, 1H); 7.83–7.86 (m, 1H); 7.98 (s, 1H). 3-Amino-6-(2-chlorophenyl)pyridazine (**3h**): white needles; mp 135°C;

R_f 0.10 (AcOEt–TEA 2%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.21 (m, 2H); 6.80 (d, $J=9.0$ Hz, 1H); 7.36 (m, 2H); 7.46 (dd, $J=6.5$ Hz, $J=2$ Hz, 1H); 7.58 (d, $J=9.0$ Hz, 1H); 7.67 (dd, $J=6.5$ Hz, $J=2$ Hz, 1H). 3-Amino-6-(4-methylphenyl)pyridazine (**3i**): white needles; mp 163°C; R_f 0.50 (AcOEt–MeOH 9:1/TEA 2%) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.41 (s, 3H); 4.80 (m, 2H); 6.82 (d, $J=9.0$ Hz, 1H); 7.29 (d, $J=7.5$ Hz, 2H); 7.62 (d, $J=9$ Hz, 1H); 7.86 (d, $J=9$ Hz, 2H). 3-Amino-6-(3-methylphenyl)-pyridazine (**3j**): white needles; mp 132°C; R_f 0.54 (AcOEt–MeOH 9:1/TEA 2%) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.44 (s, 3H); 4.77 (m, 2H); 6.83 (d, $J=9$ Hz, 1H); 7.24 (d, $J=8$ Hz, 1H); 7.37 (t, $J=7.5$ Hz, 1H); 7.64 (d, $J=9$ Hz, 1H); 7.72 (d, $J=8.0$ Hz, 1H); 7.83 (s, 1H). 3 - Amino - 6 - (2 - methylphenyl)pyridazine (**3k**): white needles; mp 126°C; R_f 0.50 (AcOEt–MeOH 9:1/TEA 2%) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.36 (s, 3H); 5.52 (m, 2H); 6.83 (d, $J=9.0$ Hz, 1H); 7.25–7.41 (m, 5H).

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