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A New Approach Towards the Synthesis of 3-Amino-6-(hetero)arylpyridazines Based on Palladium Catalyzed Cross-coupling Reactions[1]

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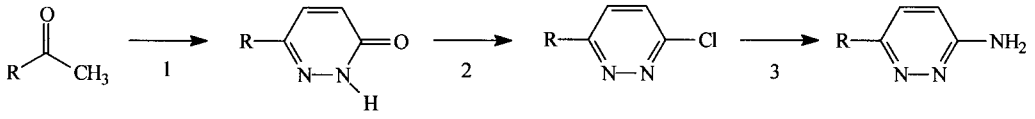
Abstract—The synthesis of 3-amino-6-(hetero)arylpyridazines via palladium catalyzed cross-coupling reactions (Suzuki, Stille) on 3-amino-6-chloropyridazine (**1a**) and 3-amino-6-iodopyridazine (**1b**) has been investigated. Comparison of the results shows that there is no need to start from **1b**. An improved method for the synthesis of compound **1b** from **1a** is also described.

The 3-aminopyridazine skeleton has proved to be interesting from a pharmacological point of view.[2–6] An important representative is Minaprine (Cantor®), a psychotropic drug developed by French researchers.[2,3,7,8] This antidepressant will certainly stimulate the search for new drugs based on the 3-aminopyridazine skeleton. An interesting group of 3-aminopyridazines are 3-amino-6-(hetero)arylpyridazines as they are intermediates for the synthesis of several pharmacologically active compounds. 6-(Hetero)arylimidazo[1,2-b]pyridazines for instance were proposed for the treatment of anxiety[9] and dementia of the Alzheimer type[10] while 3-amino-2-(3-carboxypropyl)-6-(hetero)arylpyridazinium halogenides are selective $GABA_A$ antagonists.[2,11–16] One of the most selective and potent examples of the latter is Gabazine [3-amino-2-(3-carboxypropyl)-6-(4-methoxyphenyl)pyridazinium bromide].[16]

Hitherto the 3-amino-6-(hetero)arylpyridazines were prepared in a two or three step sequence starting from the 3(2*H*)-pyridazinones (Scheme 1).[2,9,11,12,17] Reaction of the 6-(hetero)aryl-3(2*H*)-pyridazinones with $POCl_3$ gives the corresponding 3-chloropyridazines.[18] A direct amination of these 3-chloro-6-(hetero)arylpyridazines yields the desired compounds but has been stated as impractical by some authors.[2,12] The three step approach uses hydrazine as a precursor of the amino function. Hydrogenolysis of the 3-hydrazino-6-(hetero)arylpyridazines with a Raney Nickel type catalyst gives 3-amino-6-(hetero)arylpyridazines in good yields.[2,11,12,17] The hydrazine/Raney Nickel methodology, however, has some limitations. For instance sulfur containing 3-hydrazinopyridazines are not compatible with the catalyst. For the synthesis of the 6-(hetero)-aryl-3(2*H*)-pyridazinones several approaches are known in the literature.[19–26] The shortest methods require at least two reactions starting from commercially available products.[19–21] The best method hitherto available, developed by Coates and McKillop, is a one pot process based on the condensation of a methyl (hetero)arylketone with glyoxylic acid (Scheme 1).[21]

The overall yields for the synthesis of the 3-amino-6-(hetero)arylpyridazines are generally poor due to the



Scheme 1. (1) (a) $OHCCOOH{\cdot}H_2O$, solvent, (b) H_2O, NH_4OH to pH 8, (c) extraction of unreacted educt, (d) $N_2H_4.H_2O$; (2) $POCl_3$; (3) direct amination; or (3) (a) $N_2H_4{\cdot}H_2O$, and (b) Raney Nickel.

Keywords: palladium and compounds; Suzuki reactions; Stille reactions; pyridazines.
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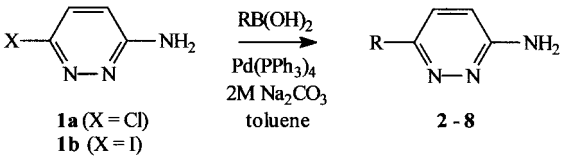
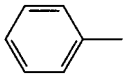
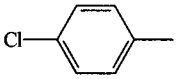
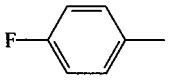
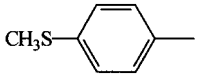
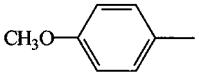
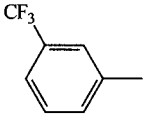
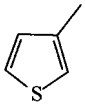
Table 1.



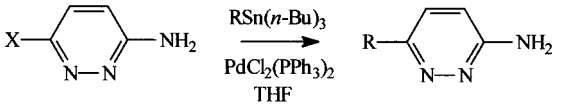
1a (X = Cl)
1b (X = I)

2 - 8

R	Reaction product	Yield from **1a** (%)	Yield from **1b** (%)
	**2**	69	68
	**3**	70	68
	**4**	84	63
	**5**	75	73
	**6**	78	92
	**7**	81	80
	**8**	74	91

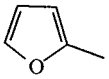
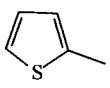
above described multistep approach. Therefore it looked very attractive to us to explore the possibilities of palladium catalyzed cross-coupling reactions (Suzuki,[27,28] Stille[29]) for the direct (hetero)arylation of commercially available 3-amino-6-chloropyridazine (**1a**). A very recent paper of Parrot et al. prompted us to now disclose our results.[30]

Table 2.

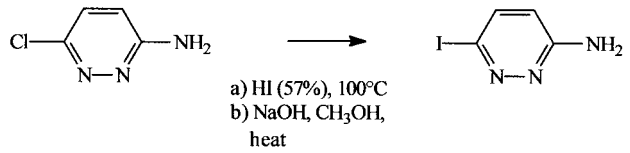


1a (X = Cl)
1b (X = I)

9 - 10

R	Reaction product	Yield from **1a** (%)	Yield from **1b** (%)
	**9**	89	99
	**10**	96	87

Our new approach gives 3-amino-6-(hetero)arylpyridazines in moderate to good yields (Tables 1 and 2). The biaryl cross-coupling reactions on **1a** of Table 2 are the first examples of Stille reactions on chloropyridazines. To our knowledge only a few papers deal with the use of palladium catalyzed biaryl cross-coupling for the synthesis of 3,6-disubstituted pyridazines.[31,32] These papers have mainly concentrated on the use of iodopyridazines.[32] Bailey et al. claim that the use of iodopyridazines is beneficial over chloropyridazines but do not give experimental proof for the Suzuki or Stille reaction.[32] They base this theory on the well documented use of the Sonogashira[33] reaction on halopyridazines.[34–37] In this reaction, chloropyridazines require more severe conditions than iodopyridazines. The harsh conditions often cause low yields for the former. The statement of Bailey prompted us to investigate cross-coupling reactions with 3-amino-6-iodopyridazine (**1b**) under the same conditions as we used for 3-amino-6-chloropyridazine (**1a**) (Tables 1 and 2). For the Stille reactions on **1b** the reaction times used for the corresponding syntheses with the chloro analogue were not sufficient. Much longer reaction times were required. Further, the yields in Tables 1 and 2 clearly show that there is no reason to use **1b** for Suzuki or Stille reactions. Even when the biaryl



Scheme 2.

cross-coupling reactions starting from **1b** give a higher yield, one has to take into account that **1b** is not commercially available and requires at least one additional synthetic step starting from the commercially available products. The known one step method for the synthesis of **1b** from **1a** seems the most attractive but the reported yield of 3-amino-6-iodopyridazine hydroiodide is less than 7%.[38] In this procedure **1a** is heated under reflux in HI solution. We turned this procedure into a high yield synthesis (83%) mainly by increasing the reaction time (Scheme 2).

Starting from the commercially available 3-amino-6-chloropyridazine (**1a**), we have demonstrated that 3-amino-6-(hetero)arylpyridazines can be easily prepared in a one step procedure. Since iodopyridazines are more expensive and generally not so easily accessible as chloropyridazines, we think that the experimental proof that there is no necessity to start from the iodo derivatives will stimulate the use of palladium catalyzed cross-coupling reactions for the direct (hetero)arylation of the pyridazine skeleton.

Experimental

^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer in DMSO-d_6, with TMS as internal standard. Chemical shifts are given in ppm and *J* values in Hz. LRMS spectra were recorded on a Ribermag R10-10B quadrupole mass spectrometer and HRMS spectra on an Autospec-oa-TOF (Micromass, Manchester, UK) at 10000 resolution with PFK as reference. IR spectra were recorded on a Bruker vector 22 spectrometer. Melting points were determined on a Büchi B-545 apparatus and are uncorrected. 3-Amino-6-chloropyridazine was purchased from Lancaster and Maybridge. The boronic acids and organostannanes were also obtained from commercial sources (Aldrich and Lancaster). THF (Acros) was dried and freshly distilled before use. The 57% HI solution (Acros) was unstabilized and used directly without purification. Flash column chromatography was performed on Kieselgel 60 (Merck), 0.040–0.063 mm.

3-Amino-6-iodopyridazine (1b). 3-Amino-6-chloropyridazine (2.0 g, 15.4 mmol) and HI (16 mL, 57%) were heated at 100°C under magnetic stirring for 20 h. After cooling, a small quantity of EtOAc was added. The suspension was placed in an ultrasonic bath for a few minutes, filtered and washed thoroughly with EtOAc. The residue was dissolved in MeOH (60 mL) and NaOH (0.65 g, 16.3 mmol) was added. This mixture was heated to reflux for five minutes. After cooling the solution was evaporated under reduced pressure to dryness. Water (70 mL) was added and the suspension violently stirred for 15 min. The solid material was filtered off and dried under vacuum yielding the title compound **1b** (2.49 g, 73%) as a light yellow solid (this material contains 2% of 3-amino-6-chloropyridazine[39]), mp 158°C. The filtrate was extracted with $CHCl_3$ (9×100 mL) and the $CHCl_3$ evaporated under reduced pressure. After drying under vacuum a second portion of 3-amino-6-iodopyridazine (0.341 g, 10%) was obtained (this material contains 3% of 3-amino-6-chloropyridazine[39]). ν_{max} (KBr): 3324 (br), 3143 (br), 1650, 1587, 1451, 1139, 1098, 1051, 833, 619 cm^{-1}; δ_H (DMSO-d_6): 6.52 (s, 2H, NH_2), 6.55 (d, 1H, *J*=9.2 Hz, H-4), 7.53 (d, 1H, *J*=9.2 Hz, H-5); LRMS (EI): 221, 193, 165, 152, 127, 94; HRMS (EI): M^+, found 220.9453, $C_4H_4IN_3$ requires 220.9450.

General procedure for the synthesis of 3-amino-6-(hetero)arylpyridazines (2–8) via Suzuki cross-coupling

A mixture of 3-amino-6-halopyridazine (**1a** or **1b**, 2.55 mmol), boronic acid (3.825 mmol), $Pd(PPh_3)_4$ (0.090 g, 0.078 mmol), toluene (15 mL) and Na_2CO_3 (2.7 mL, 2 M) was flushed with N_2 for 5 min under magnetic stirring. The reaction mixture was stirred and heated under reflux (temperature of oil bath=120°C) under a N_2 atmosphere until the starting material has disappeared. After cooling, the reaction mixture was evaporated under reduced pressure to dryness. EtOAc (80 mL) was added and the suspension was placed in an ultrasonic bath for a few minutes. The mixture was filtered, washed thoroughly with EtOAc (200 mL) and the filtrate evaporated under reduced pressure to dryness. The residue was purified by flash column chromatography on silica gel.

The following compounds were prepared in this manner.

3-Amino-6-phenylpyridazine (2). Reaction time: 23 h (starting from **1a** and **1b**); yield: 69% (from **1a**) and 68% (from **1b**); eluent for flash column chromatography: EtOAc; mp 153°C (white); ν_{max} (KBr): 3412, 3282, 3113 (br), 1647, 1459, 1441, 1136, 844, 782, 744, 698 cm^{-1}; δ_H (DMSO-d_6): 6.56 (s, 2H, NH_2), 6.90 (d, 1H, *J*=9.3 Hz, H-4), 7.40 (t, 1H, *J*=7.8 Hz, H-4′), 7.47 (t, 2H, *J*=7.8 Hz, H-3′), 7.84 (d, 1H, *J*=9.3 Hz, H-5), 7.96 (d, 2H, *J*=7.0 Hz, H-2′); LRMS (EI): 171, 143, 115, 102; HRMS (EI): M^+, found 171.0795, $C_{10}H_9N_3$ requires 171.0796.

3-Amino-6-(4-chlorophenyl)pyridazine (3). Reaction time: 15 h (starting from **1a** and **1b**); yield: 70% (from **1a**) and 68% (from **1b**); eluent for flash column chromatography: EtOAc; mp 177°C (white); ν_{max} (KBr): 3411, 3282, 3124 (br), 1645, 1595, 1448, 1140, 1098, 830 cm^{-1}; δ_H (DMSO-d_6): 6.54 (s, 2H, NH_2), 6.87 (d, 1H, *J*=9.3 Hz, H-4), 7.52 (d, 2H, *J*=8.9 Hz, H-3′), 7.83 (d, 1H, *J*=9.3 Hz, H-5), 7.99 (d, 2H, *J*=8.9 Hz, H-2′); LRMS (EI): 205, 177, 149, 136, 101; HRMS (EI): M^+, found 205.0406, $C_{10}H_8ClN_3$ requires 205.0407.

3-Amino-6-(4-fluorophenyl)pyridazine (4). Reaction time: 14 hours (starting from **1a** and **1b**); yield: 84% (from **1a**) and 63% (from **1b**); eluent for flash column chromatography: EtOAc; mp 167°C (white); ν_{max} (KBr): 3413, 3285, 3122 (br), 2925, 1647, 1602, 1510, 1451, 1236, 1160, 1136, 836 cm^{-1}; δ_H (DMSO-d_6): 6.46 (s, 2H, NH_2), 6.86 (d, 1H, *J*=9.3 Hz, H-4), 7.29 (t, 2H, *J*=9.0 Hz, H-3′), 7.80 (d, 1H, *J*=9.3 Hz, H-5), 8.00 (dd, 2H, *J*=9.0 Hz, 5.5,

H-2′); LRMS (EI): 189, 161, 133, 120; HRMS (EI): M^+, found 189.0708, $C_{10}H_8FN_3$ requires 189.0702.

3-Amino-6-(4-methylthiophenyl)pyridazine (5). Reaction time: 8 h (starting from **1a** and **1b**); yield: 75% (from **1a**) and 73% (from **1b**); eluent for flash column chromatography: EtOAc–MeOH (98:2); mp 171°C (white); ν_{max} (KBr): 3406, 3282, 3113 (br), 1649, 1595, 1451, 1142, 1096, 821 cm^{-1}; δ_H (DMSO-d_6): 2.52 (s, 3H, SCH_3), 6.44 (s, 2H, NH_2), 6.85 (d, 1H, J=9.3 Hz, H-4), 7.34 (d, 2H, J=8.7 Hz, H-3′), 7.78 (d, 1H, J=9.2 Hz, H-5), 7.91 (d, 2H, J=8.5 Hz, H-2′); LRMS (EI): 217, 202, 189, 174, 161, 148, 133; HRMS (EI): M^+, found 217.0669, $C_{11}H_{11}N_3S$ requires 217.0674.

3-Amino-6-(4-methoxyphenyl)pyridazine (6). Reaction time: 5 h (starting from **1a** and **1b**); yield: 78% (from **1a**) and 92% (from **1b**); eluent for flash column chromatography: EtOAc; mp 171°C (white); ν_{max} (KBr): 3415, 3294, 3109 (br), 1650, 1609, 1512, 1457, 1281, 1249, 1176, 1031, 826 cm^{-1}; δ_H (DMSO-d_6): 3.79 (s, 3H, OCH_3), 6.35 (s, 2H, NH_2), 6.85 (d, 1H, J=9.3 Hz, H-4), 7.00 (d, 2H, J=8.7 Hz, H-3′), 7.74 (d, 1H, J=9.3 Hz, H-5), 7.88 (d, 2H, J=8.7 Hz, H-2′); LRMS (EI): 201, 173, 158, 145, 132, 117; HRMS (EI): M^+, found 201.0902, $C_{11}H_{11}N_3O$ requires 201.0902.

3-Amino-6-(3-trifluoromethylphenyl)pyridazine (7). Reaction time: 20 h (starting from **1a** and **1b**); yield: 81% (from **1a**) and 80% (from **1b**); eluent for flash column chromatography: CH_2Cl_2–MeOH (98:2); mp 141°C (white); ν_{max} (KBr): 3354 (br), 3306 (br), 3124 (br), 1645, 1603, 1464, 1337, 1265, 1175, 1133, 1069, 1048, 845, 808, 702 cm^{-1}; δ_H (DMSO-d_6): 6.63 (s, 2H, NH_2), 6.90 (d, 1H, J=9.4 Hz, H-4), 7.71 (t, 1H, J=7.6 Hz, H-5′), 7.75 (br d, 1H, J=7.8 Hz, H-4′ or H-6′), 7.96 (d, 1H, J=9.3 Hz, H-5), 8.27 (br d, 1H, J=7.5 Hz, H-4′ or H-6′), 8.32 (br s, 1H, H-2′); LRMS (EI): 239, 220, 211, 183, 170; HRMS (EI): M^+, found 239.0670, $C_{11}H_8F_3N_3$ requires 239.0670.

3-Amino-6-(3-thienyl)pyridazine (8). Reaction time: 25 h (starting from **1a** and **1b**); yield: 74% (from **1a**) and 91% (from **1b**); eluent for flash column chromatography: EtOAc–MeOH (98:2); mp 163°C (white); ν_{max} (KBr): 3409, 3282, 3090, 1647, 1454, 1411, 1135, 847, 792, 760 cm^{-1}; δ_H (DMSO-d_6): 6.39 (s, 2H, NH_2), 6.81 (d, 1H, J=9.2 Hz, H-4), 7.60 (dd, 1H, J=5.0, 2.9 Hz, H-4′), 7.69 (dd, 1H, J=5.0, 1.4 Hz, H-5′), 7.73 (d, 1H, J=9.2 Hz, H-5), 7.96 (dd, 1H, J=2.9, 1.4 Hz, H-2′); LRMS (EI): 177, 149, 121, 108; HRMS (EI): M^+, found 177.0362, $C_8H_7N_3S$ requires 177.0361.

General procedure for the synthesis of 3-amino-6-(hetero)arylpyridazines (9–10) via Stille cross-coupling

A mixture of 3-amino-6-halopyridazine (**1a** or **1b**, 2.55 mmol), $PdCl_2(PPh_3)_2$ (0.168 g, 0.24 mmol), THF (6 mL) and organostannane (3.5 mmol) was flushed with N_2 for 5 min under magnetic stirring. The reaction mixture was stirred and heated under reflux (temperature of oil bath=85°C) under a N_2 atmosphere until the starting material has disappeared. After cooling, the reaction mixture was evaporated under reduced pressure to dryness. EtOAc (50 mL) was added and the suspension was placed in an ultrasonic bath for a few minutes. The mixture was filtered over Celite and washed thoroughly with EtOAc and the filtrate evaporated under reduced pressure to dryness. The residue was purified by flash column chromatography on silica gel. The obtained product was solved in EtOAc (50 mL) and a saturated KF solution in water (100 mL) was added. The two phase system was magnetically stirred overnight and filtered. The organic layer washed with NaOH (50 mL, 1 M), dried over $MgSO_4$ and evaporated under reduced pressure to dryness.

The following compounds were prepared in this manner.

3-Amino-6-(2-furanyl)pyridazine (9). Reaction time: 20 h (starting from **1a**), 39 h (starting from **1b**); yield: 89% (from **1a**) and 99% (from **1b**); eluent for flash column chromatography: CH_2Cl_2–MeOH (97:3); mp 134°C (yellow); ν_{max} (KBr): 3313 (br), 3156 (br), 1638, 1496, 1464, 1158, 1002, 842, 732 cm^{-1}; δ_H (DMSO-d_6): 6.52 (s, 2H, NH_2), 6.62 (dd, 1H, J=3.4, 1.7 Hz, H-4′), 6.84 (d, 1H, J=9.3 Hz, H-4), 6.97 (dd, 1H, J=3.4, 0.8 Hz, H-3′), 7.61 (d, 1H, J=9.3 Hz, H-5), 7.77 (dd, 1H, J=1.8, 0.8 Hz, H-5′); LRMS (EI): 161, 133, 104, 92; HRMS (EI): M^+, found 161.0582, $C_8H_7N_3O$ requires 161.0589.

3-Amino-6-(2-thienyl)pyridazine (10). Reaction time: 30 h (starting from **1a**), 107 h (starting from **1b**); yield: 96% (from **1a**) and 87% (from **1b**); eluent for flash column chromatography: CH_2Cl_2–MeOH (98:2); mp 139°C (yellow); ν_{max} (KBr): 3447, 3347, 3415, 3094, 1628, 1461, 1429, 1132, 841, 821, 722, 697, 681 cm^{-1}; δ_H (DMSO-d_6): 6.49 (s, 2H, NH_2), 6.83 (d, 1H, J=9.3 Hz, H-4), 7.12 (dd, 1H, J=5.0, 3.5 Hz, H-4′), 7.51 (dd, 1H, J=5.2, 1.0 Hz, H-5′), 7.56 (dd, 1H, J=3.7, 1.1 Hz, H-3′), 7.79 (d, 1H, J=9.3 Hz, H-5); LRMS (EI): 177, 149, 121, 108; HRMS (EI): M^+, found 177.0333, $C_8H_7N_3S$ requires 177.0361.

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