Expeditive Synthesis of 4-Substituted 3-Aminopyridazines

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Abstract: 3-Aminopyridazines substituted at position 4 were prepared via palladium-catalysed cross-coupling reactions starting from 3-amino-4-bromopyridazines using Suzuki and Sonogashira experimental conditions.

Key words: aminopyridazine, palladium, catalysis, arylations, arylalkylations

Substituted 3-aminopyridazines are known to possess a wide range of pharmacological activities.[1–4] Therefore, new access to these derivatives still remains of great interest for medicinal chemists.

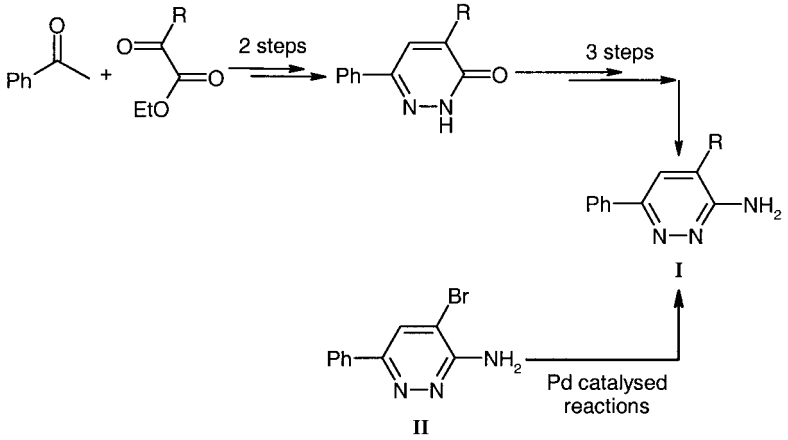
Several methods exist for the synthesis of 3-aminopyridazines. As a typical example, the preparation of 3-amino-6-phenylpyridazine substituted in position 4 (compound **I**) involved a condensation of acetophenone with an α-ketoester (Scheme 1). However, these α-ketoesters have to be synthesised first, except for the commercially available compounds (R = Me, Ph, Bn).[4,5]

As an alternative to this well-known five-step strategy (Scheme 1),[4] the use of palladium-catalysed cross-coupling reactions appeared as the most suitable approach for straightforward introduction of various substituents in position 6, mainly aromatics, [6–8] or in position 5[9,10] of the 3-aminopyridazine nucleus.

We extended the scope of this approach to position 4, as unexpected results obtained in our laboratory allowed us to prepare the 4-bromo derivative **II**, the key intermediate for palladium-catalysed cross-coupling reactions. This latter compound was prepared from the 4-nitro precursor.

4-Nitropyridazines **3a** and **3b** were prepared by nucleophilic displacement onto the 1,1-bis(thiomethyl)-2-nitroethylene **1**,[2] first by benzylamine or 2,4-dimethoxybenzylamine (DMB), and then by hydrazine hydrate (Scheme 2). Cyclocondensation of phenylglyoxal with the enamine intermediate **2** yielded two regioisomers **3** and **4**, which were separated by chromatography on silica gel.[11] The ratio of these regioisomers **3a**/**4a** and **3b**/**4b** was similar, with the 6-phenyl derivative **3** as the major product in both cases.

Surprisingly, a first treatment of 4-nitropyridazine **3a** with aqueous HBr afforded the corresponding 4-bromo derivative **5b** in poor yield (30%). Further optimisations of the experimental conditions afforded the title compounds in significantly improved yields (**5a** and **5b**, 50% and 75% respectively, reflux in a sealed tube in a 5.7 M HBr/AcOH solution, Scheme 3).[12] Under these conditions, the protecting group DMB was also removed, whereas neither drastic acid conditions nor catalytic hydrogenation were able to remove the benzyl group in compound **6**.



Scheme 1

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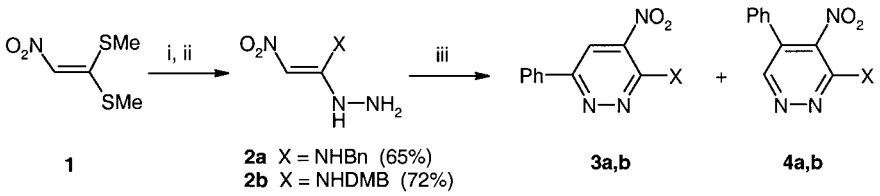
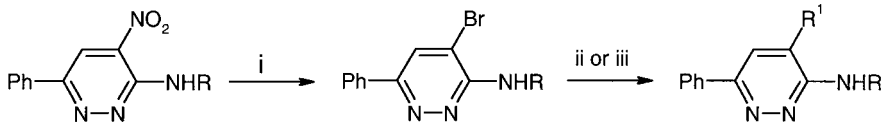


1 **2a** X = NHBn (65%) **2b** X = NHDMB (72%) **3a,b** **4a,b**

Compound	X	yield (%)	ratio
3a/4a	NHBn	76	70/30
3b/4b	NHDMB	70	60/40

Scheme 2 i) RNH_2, EtOH, reflux, 3.5 h, ii) H_2NNH_2, H_2O, EtOH, reflux, 2 h, iii) PhCOCHO, EtOH, r.t., 5 h



3a R = Bn **3b** R = DMB **5a** R = Bn **5b** R = H **6** R = Bn **7** R = H

Scheme 3 i) HBr, AcOH, sealed tube, 90 °C, 3 h, ii) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3 2 M, EtOH–toluene, iii) alkyne, $PdCl_2$, CuI, PPh_3, Et_3N, CH_3CN

Earlier studies described efficient procedures using palladium-catalysed cross-coupling reactions for introducing aryl, heteroaryl, vinyl and alkynyl groups at positions 4[13,14] and 5 [10] of pyridazinones and at position 6 of 3-aminopyridazines, [6] but to our knowledge, no report deals with a similar functionalisation at position 4 of aminopyridazines. As an illustration of the scope of the expeditive method, Suzuki [15] and Sonogashira [16] reactions were performed with various reagents (Table 1) in good yields. Alkynes **7g**–**7j** were submitted to hydrogenation (H_2, Pd/C, 75 psi, 50–75% yields) and led to novel 3-aminopyridazines bearing a functionalized aryl or alkyl chain in position 4.

Table 1 Palladium-catalysed Reactions on **5a**,**b**

Compounds	R^1	Yield of **6** (%)	Yield of **7** (%)
7a	Ph	–	85
6b,**7b**	4-MeOPh	78	70
6c,**7c**	4-ClPh	61	70
7d	2-MeOPh	–	63
7e	2-thiophenyl	–	60
7f	2-BrPh	–	92
7g	≡—TMS	–	88
6h,**7h**	≡—Ph	79	65
6i,**7i**	≡—$(CH_2)_3OBn$	40	45
7j	≡—CH_2NHBoc	–	60

In summary, the palladium-catalysed cross-coupling reaction is a new route for functionalising the position 4 of the 3-aminopyridazines without the need of any amino group protection. Moreover, this method can be generalised to other 3-substituted aminopyridazines, as the benzylamine used in Scheme 2 could be replaced by various other alkylamines.[2] These new compounds are under pharmacological evaluation as endogenous bioamine-interfering CNS agents.

References

(1) Franck, H.; Heinisch, G. *Pharmacologically Active Pyridazines*, In *Progress in Medicinal Chemistry*, Vol. 27; Ellis, G. P.; West, G. B., Eds.; Elsevier: Amsterdam, **1990**, 1–49.
(2) Contreras, J. M.; Rival, Y. M.; Chayer, S.; Bourguignon, J. J.; Wermuth, C. G. *J. Med. Chem.* **1999**, *42*, 730.
(3) Wermuth, C. G.; Bourguignon, J. J.; Schlewer, G.; Gies, J. P.; Schoenfelder, A.; Melikian, A. J. *J. Med. Chem.* **1987**, *30*, 239.
(4) Wermuth, C. G.; Schlewer, G.; Bourguignon, J. J.; Maghioros, G.; Bouchet, M.; Moire, C.; Kan, J. P.; Worms, P.; Biziere, K. *J. Med. Chem.* **1989**, *32*, 528.
(5) Sitamze, J. M.; Schmitt, M.; Wermuth, C. G. *J. Org. Chem.* **1992**, *57*, 3257.
(6) Guery, S.; Parrot, I.; Rival, Y.; Wermuth, C. G. *Tetrahedron Lett.* **2001**, *42*, 2115.
(7) Parrot, I.; Rival, Y.; Wermuth, C. G. *Synthesis* **1999**, 1163.
(8) Maes, B. U. W.; Lemiere, G. L. F.; Dommisse, R.; Augustyns, K.; Haemers, A. *Tetrahedron* **2000**, *56*, 1777.
(9) Estévez, I.; Coelho, A.; Ravina, E. *Synthesis* **1999**, 1666.
(10) Coelho, A.; Ravina, E.; Sotelo, E. *Synlett* **2002**, 2062.
(11) The structures of **3a**,**b** and **4a**,**b** were determined by ^1H and ^{13}C NMR. **3a**: Yield 53%. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.11 (d, *J* = 5.6 Hz, 2 H, CH_2Ph); 7.3–7.6 (m, 8 H, ArH); 7.99 (m, 1 H, N*H*Bn exchange with D_2O); 8.06 (m, 2 H, ArH); 8.40 (s, 1 H, H5). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 46.24

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(CH_2); 118.29 (C5); 126.37 (2 CHAr); 128.27 (CHAr); 128.44 (2 CHAr); 129.29 (2 CHAr); 129.54 (2 CHAr); 129.95 (CHAr); 132.14 (C4); 135.39 (CAr); 138.00 (CAr); 149.57 (C3); 152.13 (C6). **4a**: Yield 23%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.98 (d, *J* = 5.4 Hz, 2 H, C*H*$_2$Ph); 6.42 (m, 1 H, N*H*Bn exchange with D_2O); 7.3–7.6 (m, 10 H, ArH); 8.79 (s, 1 H, H6). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 46.56 (CH_2); 128.06 (2 CHAr); 128.25 (2 CHAr); 128.49 (2 CHAr); 129.26 (CHAr); 129.76 (2 CHAr); 130.55 (CHAr); 132.29 (C5); 133.06 (CAr); 133.34 (C4); 138.05 (CAr); 145.11 (C6); 149.46 (C3). Similar satisfactory spectral data were obtained for **3b** and **4b**.

(12) Structures of compounds **3a** and **4a** have been unambiguously assigned by hsqc experiments: strong correlations have been observed between C3 and CH_2Ph and between C3 and C5H for compound **3a**, whereas no correlation could be observed between C3 and C6-H for compound **4a** (Figure 1).

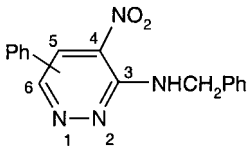

Figure 1

Representative procedure for the preparation of 5a,b from 3a,b. To a solution of 3-substituted amino-4-nitro-6-phenylpyridazine **3a**,**b** (1.36 mmol) in acetic acid (8 mL) was added 720 mL of a 5.7 M solution of HBr–AcOH (4.10 mmol, 3 equiv). The mixture was then heated at 90 °C in a sealed tube during 3 h. The solvent was evaporated and the crude oil was purified by flash chromatography (EtOAc–hexane, 1:2). **5b**: Yield 75%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.61 (br s, 2 H, N*H*$_2$ exchange with D_2O); 7.3–7.5 (m, 3 H, ArH); 7.80 (s, 1 H, H5); 7.8–7.9 (m, 2 H, ArH). ESMS *m*/*z*: 250 (M^+, ^{79}Br), 252 (M^+, ^{81}Br). Similar satisfactory spectral data were obtained for **5a**.

(13) Maes, B. U. W.; R'kyek, O.; Kosmrlj, J.; Lemiere, G. L. F.; Esmans, E.; Rozenski, J.; Dommisse, R.; Haemers, A. *Tetrahedron* **2001**, *57*, 1323.

(14) Maes, B. U. W.; Monsieurs, K.; Loones, K. T. J.; Lemiere, G. L. F.; Dommisse, R.; Matyus, P.; Riedl, Z.; Hajos, G. *Tetrahedron* **2002**, *58*, 9713.

(15) **Representative procedure for Suzuki arylations**. A suspension of **5a** or **5b** (0.60 mmol, 1 equiv), phenylboronic acid (0.69 mmol, 1.15 equiv), sodium carbonate 2 M (0.64 mL, 1.27 mmol, 2.12 equiv) in toluene (1.8 mL) and ethanol (0.2 mL) was stirred under an atmosphere of argon for 30 min. $Pd(PPh_3)_4$ (0.027 mmol, 0.045 equiv) was then added and the mixture was heated at 110 °C for 20 h. The toluene was removed in vacuo, the residue was 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 on silica gel (for compounds **6**: EtOAc–hexane 1:2; for compounds **7**: EtOAc–hexane 1:1, TEA 2%). Satisfactory spectral data were obtained for all new compounds. As an example **7b**: mp 167–169 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.93 (s, 3 H, OC*H*$_3$); 5.02 (br s, 2 H, N*H*$_2$ exchange with D_2O); 7.10 (d, *J* = 8.3 Hz, 2 H, ArH); 7.4–7.5 (m, 5 H, ArH); 7.55 (s, 1 H, H5); 8.04 (d, *J* = 8.2 Hz, 2 H, ArH).

(16) **Representative procedure for Sonogashira couplings**. A mixture of **5a** or **5b** (0.76 mmol, 1 equiv), alkyne (1.14 mmol, 1.5 equiv), $Pd(PPh_3)_2Cl_2$ (0.076 mmol, 0.1 equiv), CuI (0.076 mmol, 0.1 equiv) and dry triethylamine (0.158mL, 1.14 mmol, 1.5 equiv) in dry acetonitrile (5 mL) was flushed with argon for 5 min. The reaction mixture was heated at 70 °C for 12 h. The solution was concentrated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel (for compounds **6**: EtOAc–hexane 1:3; for compounds **7**: EtOAc–hexane 1:1, Et_3N 2%). Satisfactory spectral data were obtained for all new compounds. As an example **6i**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.93 (m, 2 H, C*H*$_2$); 2.64 (t, *J* = 6.9 Hz, 2 H, C*H*$_2$); 3.59 (t, *J* = 6.8 Hz, 2 H, C*H*$_2$); 4.49 (s, 2 H, OC*H*$_2$Ph); 4.90 (d, *J* = 5.6 Hz, 2 H, NHC*H*$_2$Ph); 5.50 (t, *J* = 5.6 Hz, 1 H, N*H* exchange with D_2O); 7.3–7.5 (m, 13 H, ArH); 7.59 (s, 1 H, H5); 8.00 (m, 2 H, ArH).

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