

Palladium-catalysed amination of 2-acyl-1-alkyl-5-bromopyrroles [☆]

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Abstract—The first intermolecular C–N bond-forming reactions between substituted 2-bromopyrroles and primary and cyclic secondary amines were performed using Pd₂(dba)₃ as catalyst with BINAP as the ligand. The aminations proceeded in the presence of NaO^tBu at 80–100 °C in 31–93% yields.

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In conjunction with our recent work on the chemistry and biology of pyrrolodiazines^{1–4} we had to prepare a series of dihydropyrrolo[1,2-*a*]pyrazine derivatives of general structure **1** (Fig. 1). As it was envisaged that a palladium-catalysed amination of the appropriate haloheterocycle would provide the desired series, we needed to investigate the palladium-catalysed amination of the pyrrole moiety.

Although palladium-catalysed carbon–nitrogen bond formation using aryl halides has been extensively investigated in recent years,^{5–8} allowing the coupling of a great variety of amines with any halobenzene or haloazine, no broadly applicable methodology had been developed to prepare five-membered heterocycles^{9,10} until very recently when Hartwig reported the successful amination of halofurans, -thiophenes, -thiazoles, -oxazoles, -indoles and -benzimidazoles.¹¹ However, the methodology was not extended to halopyrroles because of the instability of these substrates. Herein we wish to report our progress in the Pd-catalysed cross coupling reaction between functionalised 2-bromopyrroles **2** and **3** and a selection of primary and secondary amines.

As a starting point, it is noticeable that all our attempts to carry out the amination reaction between morpholine and either 2- or 3-bromopyrrole failed both with the

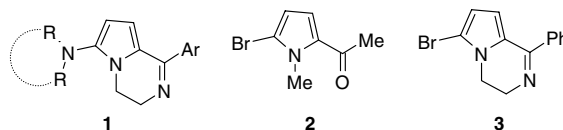


Figure 1.

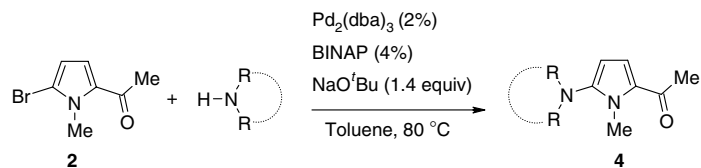
parent heterocycle and a protected model (Me, TIPS).¹² Thus we selected 2-acetyl-5-bromo-1-methylpyrrole **2**¹³ as the simplest model to establish the most effective conditions for the C–N bond formation.

Initially, the reaction between **2** and morpholine was tested using Pd₂(dba)₃ as catalyst in the presence of different ligands such as dppf, BINAP, P^tBu₃ and biphenyl P^tBu₂. Using a strong base such as NaO^tBu in THF, the dppf ligand failed to form any coupled product whereas in toluene P^tBu₃ and biphenyl P^tBu₂ produced low or moderate yields. Racemic BINAP appeared to be the ligand, which afforded the best yield¹⁴ in combination with NaO^tBu (weaker bases such as CsCO₃ and K₃PO₄ were also tested) in toluene at 80 °C. Using the optimised conditions shown in Scheme 1 a variety of cyclic secondary amines (Table 1, entries 1–6) were successfully coupled with substrate **2** with yields shown in Table 1. However, when the above optimised conditions were applied to the coupling reaction of **2** and acyclic secondary amines such as di-*n*-butylamine, diphenylamine and dipropenylamine, no reaction was observed. An alternative study of the reaction conditions for the coupling of di-*n*-butylamine and **2** using the same ligands in combination with Pd(OAc)₂ or Pd(dba)₂ was also unsuccessful.

Keywords: Palladium; Catalysed; Amination; Functionalised; 2-Halopyrroles.

[☆] Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2003.11.029](https://doi.org/10.1016/j.tetlet.2003.11.029)

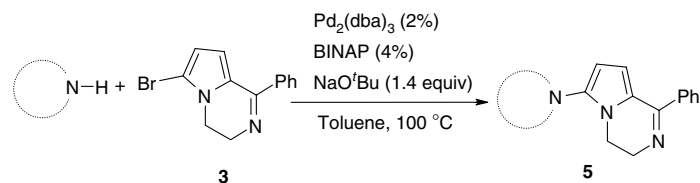
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Scheme 1.

Table 1. Palladium-catalysed amination of 2-acetyl-5-bromo-1-methylpyrrole (**2**)

Entry	Amine	Coupling product (4)	Yield (%)
1			73
2			65
3			93
4			85
5			69
6			80
7			0
8			82
9			48
10			50
11			45
12			31



Scheme 2.

Table 2. Palladium-catalysed amination of 6-bromo-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (**3**)

Entry	Amine	Coupling product (5)	Yield (%)
1			69
2			64
3			69
4			45
5			43
6			51

In contrast with the lack of reactivity of di-*n*-butylamine, primary amines did react with **2** under the same conditions used for cyclic secondary amines, affording the corresponding coupled products in good (Table 1, entry 8) or moderate yields (Table 1, entries 9–12).¹⁵ These isolated yields were moderate at least in part because of the difficulties of isolation of the amines **4** (Table 1, entries 9–12).

The large difference in reactivity of substrate **2** with the selection of amines tested was also found with 6-bromo-1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine **3**.¹⁶ In fact, this substrate only reacted with cyclic secondary amines, affording compounds **5** shown in Table 2. No acyclic secondary or primary amine reacted under the conditions employed for the successful coupling of cyclic secondary amines or under any of the other conditions tested [Pd(dba)₂ or Pd(OAc)₂ and P^tBu₃, ferrocenyl di-*tert*-butylphosphine, biphenyl P^tBu₂ or dppf], with substrate **3** being recovered unaltered or as the debrominated compound (Scheme 2). It is noteworthy that in this case the yields of amination using cyclic secondary amines were strongly dependent on the reaction tem-

perature, with heating at 100 °C (instead of 80 °C used for substrate **2**) affording the best isolated yields.¹⁷

In summary, we have studied the conditions for the amination of 6-bromo-1-phenyl-3,4-dihydro-pyrrolo[1,2-*a*]pyrazine using 2-acetyl-5-bromo-1-methylpyrrole as a simple model for the palladium-catalysed amination, which occurred in the presence of Pd₂(dba)₃, BINAP and NaO^tBu in toluene at 80–100 °C. This procedure allowed for, the first time, the amination of substituted 2-halopyrroles with cyclic secondary and primary amines. Work is in progress to extend this methodology to a variety of substituted 2- and 3-halopyrroles.

Acknowledgements

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- Both racemic and *R*-(+)-BINAP give the same yields in the amination reaction.
- General procedure for the reaction of **2**. An oven-dried glass vial was charged with **2** (1.0 mmol), 1.2 mmol (entries 1–8, 10) or 3.0 mmol (entries 9, 11, 12) of the amine, NaO^tBu (1.4 mmol), Pd₂(dba)₃ and (0.02 mmol), and BINAP (0.04 mmol), in dry toluene (2 mL) under argon. The flask was immersed in an oil bath heated at 80 °C and stirred overnight. The solution was then allowed to cool to room temperature, taken up in CH₂Cl₂ (10 mL), filtered over Celite and concentrated. Column chromatography of the residue on silica gel using EtOAc as eluent gave pure compounds **4**.
- This compound was prepared (Castellote, I. Ph.D. Thesis, University of Alcalá, 2001) by bromination with NBS (1.5 mmol, CH₂Cl₂) of the corresponding 1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine, which was obtained following the method described by Flament, I.; Sonney, P.; Ohloff, G. *Helv. Chim. Acta* **1997**, *60*, 1872. (**3**): Mp 84–86 °C; IR (KBr) ν_{\max} (cm⁻¹): 2947, 1589, 1566, 1408, 1036. ¹H NMR (300 MHz, DMSO-*d*₆) δ (ppm) 7.72–7.69 (m, 2H); 7.43–7.40 (m, 3H); 6.37 (d, 1H, *J* = 4.0 Hz); 6.23 (d, 1H, *J* = 4.0 Hz); 4.04–3.92 (m, 4H). ¹³C NMR (50 MHz, CDCl₃) δ (ppm) 159.8, 137.5, 128.4, 128.3, 125.8, 113.2, 110.8, 106.4, 48.0, 40.2; Anal. Calcd for C₁₃H₁₁BrN₂; C, 56.75; H, 4.03; N, 10.18. Found: C, 56.49; H, 4.23; N, 10.11.
- General procedure for the reaction of **3**. An oven-dried glass vial was charged with **3** (1.0 mmol), 1.2 mmol of the amine, NaO^tBu (1.4 mmol), Pd₂(dba)₃ and (0.02 mmol), and BINAP (0.04 mmol) in dry toluene (2 mL) under argon. The flask was immersed in an oil bath heated at 100 °C and stirred overnight. The solution was then allowed to cool to room temperature, diluted with water (15 mL) and extracted with CH₂Cl₂ (3 × 15 mL). The organic phase was dried (Na₂SO₄), concentrated in vacuo and the residue chromatographed on silica gel. Compounds **5** were isolated using CH₂Cl₂/MeOH (8:2) saturated with ammonia as eluent.