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Palladium catalysed amination of electron deficient halothiophenes

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Abstract

A range of functionalised aminothiophenes has been prepared via palladium-catalysed aminations. The reaction proceeds in high yield when the halide is conjugated to an electron-withdrawing group and is suitable for a wide variety of amines.

Functionalised thiophenes form an integral part of numerous natural products[1] and pharmaceuticals.[2] They are often used within medicinal chemistry as phenyl ring isosteres, allowing fine tuning of the properties of potential drug molecules.[3] As part of a drug discovery program, we required a diverse range of stable secondary- and tertiary-aminothiophenes. These needed to contain useful functionality, both appended onto the nitrogen and on the aryl ring itself, to allow further molecular diversification. No broadly applicable methodology existed for the synthesis of this class of compound. The Gewald reaction is the most well established route,[4] but is limited to the synthesis of 2-aminothiophenes containing very unreactive primary-amines (often vinylogous amides) which are difficult to functionalise further. Certain halothiophenes undergo nucleophilic aromatic substitution with amines, however this reaction is limited to very electron deficient aromatics containing nitro- and occasionally aldehyde-substituents.[5] The palladium-catalysed amination of halobenzenes has been thoroughly delineated over the last decade, primarily by the groups of Buchwald[6] and Hartwig,[7] allowing the coupling of most classes of amine with virtually any halobenzene. Application of this methodology to other heterocyclic aromatics is still relatively unexplored.[8] Watanabe recently reported the first Pd-catalysed bromothiophene amination, showing that relatively electron rich mono- and di-bromothiophenes could be coupled with diarylamines using a $Pd(OAc)_2/P(^tBu)_3$ catalyst system.[9] These reactions required a strong base (NaO^tBu) at 120°C, making them incompatible

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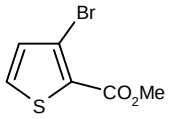
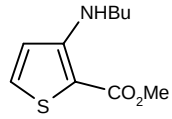
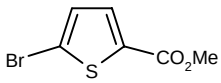
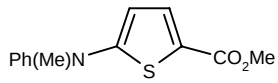
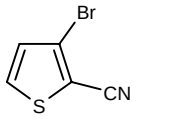
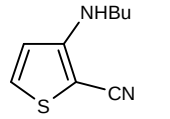
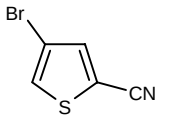
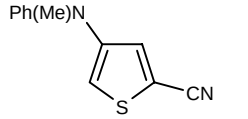
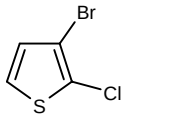
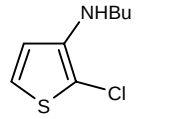
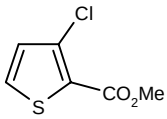
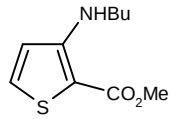
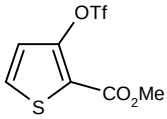
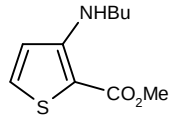
with the broader range of functionality we required. To the best of our knowledge, this is the only reported application of Pd-catalysed amination methodology to halothiophenes. Herein we detail initial Pd-catalysed cross coupling results obtained with functionalised halothiophenes and a broad selection of useful amines.

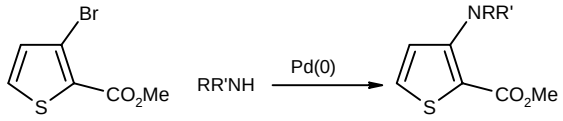
The cross coupling of 3-bromothiophene-2-carboxylic acid methyl ester with *n*-butylamine was selected for optimisation of reaction conditions. Palladium source, ligand, solvent, base, temperature and stoichiometry were optimised, eventually leading to the General Conditions A which afforded a 94% isolated yield of the expected product (Table 1, entry 1).[10] Several details are worthy of comment. Firstly, no reaction occurred in the absence of catalyst. BINAP was a superior ligand to other chelating phosphines such as DPPF and DPPP. In addition to Pd_2dba_3, $Pd(OAc)_2$ was also an effective palladium source, crucial in couplings of some of our other halothiophenes (vide infra). Toluene and dioxane were useful solvents. No other metal carbon-

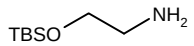
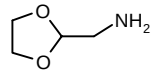
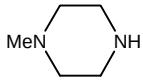
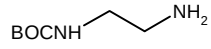
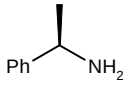
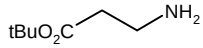
Table 1
Palladium-catalysed amination halothiophenes

Entry	Thiophene	Amine	Product	Conditions[a]	Yield[b]
1		$BuNH_2$		A	94 (100)
2		PhNHMe		B	78 (85)
3		$BuNH_2$		A	89 (100)
4		PhNHMe		A or B	- (0)
5		$BuNH_2$		A	- (7)
6		$BuNH_2$		A or B	- (68)
7		$BuNH_2$		A or B	- (96)

(a) Reaction conditions: 1.0 eq thiophene, 1.2 eq amine, 1.4 eq Cs_2CO_3, 5 Mol% Pd_2dba_3 (*General Conditions A*) or 10 Mol% $Pd(OAc)_2$, (*General Conditions B*), 10 Mol% BINAP, toluene (0.1 M), 110 °C, 20 h under N_2.
(b) Isolated yield of compounds >95% pure by HPLC analysis, GC yield in parenthesis.

Table 2
Pd-catalysed amination of 3-bromothiophene-2-carboxylic acid methyl ester[a]



Entry	Amine	Yield[b]	Entry	Amine	Yield[b]
1	$PhNH_2$	98 (100)	6	$^tBuNH_2$	40 (50)[c]
2	PhNHMe	- (100)	7		67 (72)
3	BnNHMe	- (83)	8		93 (-)
4		- (100)	9		83 (-)
5		92 (-)	10		85 (100)
			11	Et_2NH	- (19)[d]

(a) Reaction conditions: General conditions A (see table 1).
(b) Isolated yield of compounds >95% pure by HPLC analysis, GC yield in parenthesis.
(c) 36 h. (d) 40% DPPF used in place of BINAP.

ate or tertiary amine base was as effective as caesium carbonate, and stronger bases (NaO^tBu) resulted solely in amide formation. Finally, later experiments showed similar levels of conversion could be obtained in the presence of catalyst loadings down to 0.1 mol% Pd.

Aminations of a range of other halothiophenes were investigated[11] (Table 1). The structure of the halothiophene was found to have a profound effect on the reaction yield. When the halogen is conjugated to the electron-withdrawing group (2,3- or 2,5-isomers) an excellent yield of the desired product is obtained (entries 1–3). Surprisingly, changing the palladium source to $Pd(OAc)_2$ (General Conditions B), lead to vastly improved reaction yields with the 2,5-isomer. By contrast, the coupling reaction of the 2,4-isomer completely fails (entry 4). Moderately electron deficient thiophenes are required (entry 5), and finally, chloride and triflate are both useful leaving groups in this reaction (entries 6–7). Our ability to synthesise moderately electron deficient aminothiophenes for the first time compliments the results of Watanabe[9] (more electron rich analogues), and nucleophilic aromatic substitutions[5] (highly electron deficient analogues).

Table 2 shows the cross coupling results obtained with 3-bromothiophene-2-carboxylic acid methyl ester and a diverse selection of amines.[12] Virtually all classes of amine were successfully coupled in excellent yield. The reaction was relatively inert to steric encumbrance within the amine component (entries 1–6), and only when ^{t}butylamine was used did the reaction rate slow significantly. A wide range of functionality useful for further elaboration was well tolerated (entries 7–10). The only obvious limitation was our inability to couple secondary acyclic amines in high yield (entry 11). These have also been the most demanding examples in the analogous reaction of the halobenzenes, requiring the development of new ligand systems. Unfortunately, these ligands (such as PPFA[6a] and (o-biphenyl)PCy_2 [6c]), as well as more established catalytic

systems, were all equally ineffective with the halothiophenes investigated. The best conversion (19%) we have been able to achieve with diethylamine utilised DPPF as the ligand, however the reaction also afforded significant quantities of the desbromothiophene dimer (entry 11). The failure of the less electron releasing ligand (PPFA) may be attributable to its poor performance when coupling secondary amines with *ortho*-substituted aryl bromides.[13] The failure of the more electron rich ligand (*o*-biphenyl)PCy_2) may be due to the fact that it would be expected to reduce the acidity of NH proton in the ArPd(II)Br-amine catalytic intermediate, perhaps inhibiting its removal by the weaker caesium carbonate base.[14]

In conclusion, we have shown for the first time that the palladium catalysed amination of electron deficient halothiophenes is a generally useful reaction for the synthesis of a broad range of functionalised aminothiophenes. These results compliment those obtained previously with more electron rich thiophenes and give access to a number of building blocks useful within the pharmaceutical industry. Future work will include efforts to circumvent the current limitations (non-conjugated halides and secondary acyclic amines) and will be reported in due course.

Acknowledgements

We thank Professor Nigel Simpkins and Dr. Steve Clark (University of Nottingham) for their interest in this project.

References

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8. For halopyridines see references 6a,c.
9. Watanabe, M.; Yamamoto, T.; Nishiyama, M. *J. Chem. Soc., Chem Commun*. **2000**, 133–134.
10. General Conditions A: To the halothiophene (1 mmol), Cs_2CO_3 (1.4 mmol), $Pd_2(dba)_3$ (0.05 mmol, 10 mol% Pd) and BINAP (0.1 mmol, 10 mol%) under nitrogen were added toluene (10 ml) followed by the amine (1.2 mmol), and the reaction was stirred at 110°C for 20 h. After cooling to room temperature (and GC–MS analysis), the reaction mixture was pre-absorbed onto silica and purified by flash chromatography to yield the aminothiophene product. For Table 1, entry 1, flash chromatography (33% DCM in *iso*-hexane) afforded 3-butylaminothiophene-2-carboxylic acid methyl ester as a colourless oil (201 mg, 94%). IR: *v*max 1663 cm^{-1}. ^1H NMR: (300 MHz, $CDCl_3$) δ 7.32 (1H, d, $J=6$ Hz), 6.75 (1H, s), 6.63 (1H, d, $J=6$ Hz), 3.81 (3H, s), 3.26 (2H, q, $J=7$ Hz), 1.56–1.66 (2H, m), 1.41 (2H, sextet, $J=7$ Hz), 0.95 (3H, t, $J=7$ Hz). MS (EI): m/z 213 (M^+). HRMS: calcd for $C_{10}H_{15}NO_2S$: 214.0902. Found: 214.0910. General Conditions B were as A but used $Pd(OAc)_2$ (10 mol%) as the palladium source.
11. Isolated yields refer to pure compounds (>95% by HPLC) characterised by NMR, IR, HPLC–MS and combustion analysis (solids) or HRMS (oils).

12. Initial experiments reveal these amines react similarly with the corresponding 2-bromothiophene-5-carboxylic acid methyl ester.
13. This effect was originally noted for the analogous PPF–OMe ligand: Marcouw, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568–1569.
14. Some indirect evidence for this does exist—Hartwig found when using the electron rich ligand ($P(^tBu)_3$) to mediate Pd-catalysed coupling between *p*-bromotoluene and dibutylamine the reaction proceeded in 4 h at room temperature with a strong base (NaO^tBu), whereas with caesium carbonate the reaction required 12 h at 100°C (see reference 7b).