Tetrahedron Letters 53 (2012) 403–405

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Expanded scope of heterocyclic biaryl synthesis via a palladium-catalysed thermal decarboxylative cross-coupling reaction

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ARTICLE INFO

Article history:
Received 27 June 2011
Revised 28 October 2011
Accepted 11 November 2011
Available online 22 November 2011

Keywords:
Cross-coupling
Palladium
Heterocycles
Biaryls
Aryl halides

ABSTRACT

The palladium-catalysed decarboxylative cross-coupling of heterocyclic aromatic carboxylates and aryl halides is described. The cross-coupling proceeds under relatively mild conditions using catalytic Pd(0) and tetrabutylammonium bromide (TBAB). Utilizing a mixed solvent system consisting of *N*,*N*-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP), the cross-coupling system operated at temperatures ranging from 80 to 140 °C.

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The metal-catalysed decarboxylative cross-coupling of aryl halides and triflates with arene carboxylic acids has received considerable attention recently as an attractive tool for biaryl formation.[1–15] In contrast to traditional coupling methods, the decarboxylative coupling process eliminates the need to prepare organometallic reagents, which require the use of a stoichiometric amount of expensive organometallic compounds. In addition, the carboxylic acid coupling partners are more readily available when compared to their organometallic counterparts. Current reported applications of the palladium-catalysed decarboxylative coupling reaction often involve copper as a co-catalyst or require microwave technology, and generally temperatures of 130−170 °C are necessary to promote the reaction.

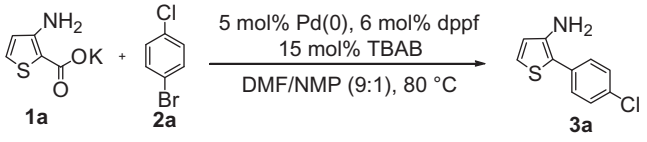
We previously described the synthesis of multigram quantities of 3-amino-2-(4-chlorophenyl)-thiophene via a decarboxylative cross-coupling using potassium 3-aminothiophene-2-carboxylate (**1a**) and 4-bromochlorobenzene (**2a**) as the coupling partners.[16]

Optimisation of the reaction led to a robust decarboxylative cross-coupling at 80 °C with catalytic (5 mol %) palladium(0) and catalytic TBAB (15 mol %) in a 9:1 DMF/NMP solvent mixture, affording **3a** in 77% yield on a 0.5 mol scale (Scheme 1).[16]

Having established the optimum conditions for the decarboxylative cross-coupling of **1a** and **2a**, we investigated the scope and generality of the reaction. Herein is described the palladium-catalysed decarboxylative cross-coupling of a range of heterocyclic aromatic carboxylates and aryl halides.

The effect of varying the aryl halide coupling partner was examined first, by reacting 1.05 equiv of potassium 3-amino-2-thiophene carboxylate (**1a**) with 1 equiv of a range of aryl halides, 5 mol % $PdCl_2$, 6 mol % dppf and 15 mol % TBAB in a 9:1 DMF–NMP mixture. The biaryl products **3b**–**3f** were isolated as the hydrochloride salts in yields ranging from 57–82%, or as the free amines in yields of 31–62% following chromatographic purification. Table 1 summarises the results of these experiments.[17]

Replacing the electron-withdrawing chlorine in 4-bromochlorobenzene with the electron-donating methoxy group in 4-bromoanisole led to a reduction in the reactivity in the cross-coupling reaction with **1a** (Table 1, entry 1). The introduction of the inductively electron-donating methyl group at the *para* position also led to a decrease in the reactivity compared to 4-bromochlorobenzene (Table



Scheme 1. Optimised conditions for cross-coupling of **1a** and **2a**.

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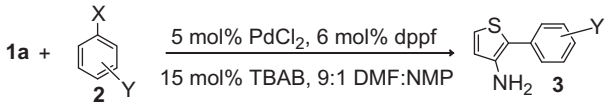
doi:10.1016/j.tetlet.2011.11.051

Table 1
Variation of the aryl halide



Entry	Aryl halide	*T* (°C)	Product	% Yield (free base)[a]	% Yield (HCl salt)
1	4-bromoanisole (**2b**)	120	**3b**	40	64[b]
2	4-bromotoluene (**2c**)	120	**3c**	62	76[b]
3	4-iodotoluene (**2d**)	100	**3d**	36	57[b]
4	bromobenzene (**2e**)	90	**3e**	46	76[b]
5	3-nitrobromo benzene (**2f**)	80	**3f**	–	59[c]
6	1-chloro-4-iodobenzene (**2g**)	100	**3g**	47	48[b]
7	3-bromoanisole (**2h**)	120	**3h**	31	82[b]

[a] Yield following chromatographic purification.
[b] Crude yield.
[c] Yield following isolation of the hydrochloride salt and subsequent purification by slurrying the product in acetone.

1, entry 2). 4-Iodotoluene was found to be more reactive than 4-bromotoluene (entry 3, Table 1), while the cross-coupling of **1a** with bromobenzene proceeded to completion at 90 °C (Table 1, entry 4). 3-Nitrobromobenzene was found to have similar reactivity to 4-bromochlorobenzene, with complete consumption of the halide at 80 °C (Table 1, entry 5). The use of 1-chloro-4-iodobenzene led to a slight reduction in the rate of the cross-coupling reaction compared to 4-bromochlorobenzene (Table 1, entry 6). Finally the effect of varying the position of the substituent on the aryl halide was investigated; 3-bromoanisole was selected for this study as 4-bromoanisole had proved to be much less reactive than 4-bromochlorobenzene and we were interested in determining if changing the position of the electron-donating methoxy group would increase the reactivity. 3-Bromoanisole was found to be similar in reactivity to 4-bromoanisole (Table 1, entry 7).

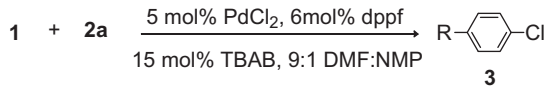
The effect of varying the carboxylate salt was also investigated. Table 2 summarises the results of these studies.

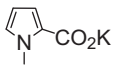
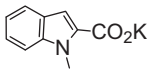
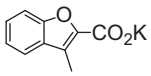
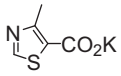
Each of the carboxylate salts examined proved to be much less reactive than potassium 3-aminothiophene-2-carboxylate (**1a**) in decarboxylative cross-coupling reactions with 4-bromochlorobenzene at temperatures of 100–150 °C (cf. 80 °C in the analogous coupling with **1a**). In all cases, the ^{1}H NMR spectra of the crude products were complex mixtures, and attainment of analytically pure samples of the cross-coupled products was difficult. In some instances, incomplete consumption of 4-bromochlorobenzene was observed (Table 2, entries 2 and 3), however when the temperature was increased to 140 °C additional side-product formation was detected.

The mechanism of this decarboxylative cross coupling is believed to involve oxidative addition of aryl halides to the Pd(0) species (prepared in situ from $PdCl_2$dppf), followed by anion metathesis to the resulting Pd(II) species with the elimination of KBr. Decarboxylation followed by reductive elimination gives the desired biaryl product (see Fig. 1). Concomitant decarboxylation and product formation supports the proposed pathway.[16] In contrast to other proposed mechanisms,[14] our system produces stoichiometric CO_2 only when both coupling partners are present. Our observations are consistent with the mechanism proposed by Forgione.[15]

Interestingly, while cross-coupling has been effected across a range of different substituents in modest yields, in all instances except **3f** the reaction temperatures required were higher than that described for the optimised procedure for the synthesis of **3a** described in our earlier report.[16] However, the reaction temperatures

Table 2
Variation of the carboxylate salt



Entry	RCO_2K	*T* (°C)	Product	Outcome[a]	Yield[b] (%)
1	 **1b**	100	**3i**	Complete reaction	25
2	 **1c**	120	**3j**	Incomplete reaction, **2a** remaining	17
3	 **1d**	120	**3k**	Incomplete reaction, 30% **2a** remaining	31
4	 **1e**	140	**3l**	Complete reaction	11

[a] By ^{1}H NMR spectroscopy.
[b] Yield following purification by chromatography on silica gel.

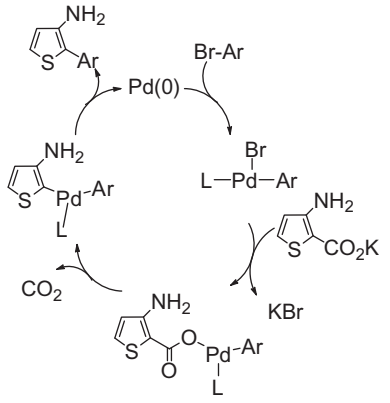


Figure 1. Proposed mechanistic pathway for decarboxylative cross-coupling.

of 80–150 °C are notably lower than most reports in the literature for cross-couplings of this nature. Thus, a decarboxylative cross-coupling has been demonstrated on a variety of heterocyclic carboxylic acids and aryl halides, using catalytic amounts of Pd(0) and TBAB at relatively low temperatures of 80–140 °C, and avoiding the use of a metal co-catalyst or microwave irradiation.

Acknowledgment

Enterprise Ireland is acknowledged for financial support for M.K. and O.A.McN.

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17. Representative Experimental Procedure: **Preparation of 2-(4-Methoxyphenyl)thiophenyl-3-amine** (**3b**) *Method A.* Potassium 3-aminothiophene-2-carboxylate (**1a**) (0.95 g, 5.25 mmol), 4-bromoanisole (0.63 mL, 5.00 mmol), TBAB (0.25 g, 0.75 mmol), 1,1′-bis(diphenylphosphino)-ferrocene (0.16 g, 0.3 mmol) and $PdCl_2$ (44.78 mg, 0.25 mmol) were mixed under a flow of N_2. The vessel was evacuated and back-filled three times. DMF (18 mL) and NMP (2 mL) were added and the system was again evacuated and back-filled with N_2 three times. The resulting mixture was heated at 120 °C for 16 h. The mixture was allowed to cool to room temperature. Celite (~1 g) and H_2O (50 mL) were added and following stirring for 10 min, the mixture was filtered through a bed of Celite. The Celite cake was washed with EtOAc (50 mL). The filtrate was transferred to a separating funnel, and the layers separated. The aqueous layer was extracted with EtOAc (50 mL). The EtOAc layers were combined and washed with H_2O (4 × 50 mL) and brine (2 × 50 mL), dried, filtered and concentrated at reduced pressure. Following purification by column chromatography on silica gel using hexane–EtOAc (gradient elution 0–20% EtOAc), **3b** was isolated as a yellow oil (0.41 g, 40%); ν_{max}/cm^{-1} 3346, 1608, 1561, 1510; δ_H (300 MHz, $CDCl_3$) 3.71 (2H, br s, NH_2), 3.84 (3H, s, OCH_3), 6.65 (1H, d, *J* 5.4, Ar*H*), 6.95 (2H, d, *J* 9.0, Ar*H*), 7.08 (1H, d, *J* 5.4, Ar*H*), 7.44 (2H, d, *J* 9.0, Ar*H*); δ_C (75.5 MHz, $CDCl_3$) 55.4 (CH_3, OCH_3), 114.5 (CH, ArCH), 116.7 (C, ArC), 122.0, 122.8 (2×CH, ArCH), 126.7 (C, ArC), 129.1 (CH, ArCH), 139.9 (C, ArC), 158.3 (C, ArC); HRMS (ES+): Exact mass calculated for $C_{11}H_{12}NOS$ [$(M+H)^+$], 206.0640. Found 206.0631; *m*/*z* (ES+) 206.0 {[$(M+H)^+$], 52%}.
Method B. Compound **3b** was also isolated as the hydrochloride salt, using the same procedure outlined above. After drying, the organic layer was concentrated to approximately 10 mL. An HCl solution (6 mL of a 1.75 M HCl solution in EtOAc) was added dropwise at 0 °C. A brown solid precipitated from the solution almost immediately. The mixture was stirred at 0 °C for 30 min. The brown solid was filtered to give the hydrochloride salt of **3b** (0.77 g, 64%). An analytically pure sample was obtained by slurrying the crude product in acetone (5 mL) at room temperature for 10 min, to give the hydrochloride salt of **3b** as an off-white solid (0.35 g, 29%); ν_{max}/cm^{-1} 2806, 1610, 1578, 1511; δ_H (300 MHz, DMSO-d_6) 3.83 (3H, s, OCH_3), 7.09 (2H, d, *J* 8.7, Ar*H*), 7.24 (1H, d, *J* 5.7, Ar*H*), 7.62 (2H, d, *J* 8.7, Ar*H*), 7.66 (1H, d, *J* 5.7, Ar*H*); δ_C (75.5 MHz, DMSO-d_6) 55.3 (CH_3, OCH_3), 114.6 (CH, ArCH), 123.2, 123.5 (2×C, ArC), 125.0, 125.2, 129.9 (3×CH, ArCH), 134.8, 159.6 (2×C, ArC); HRMS (ES+): Exact mass calculated for $C_{11}H_{12}NOS$ [$(M+H)^+$-HCl], 206.0640. Found 206.0632; *m*/*z* (ES+) 206.0 {[$(M+H)^+$-HCl], 42%}.