Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 581–585
Tetrahedron Letters

Suzuki coupling reaction for the solid-phase preparation of 5-substituted nicotinic acid derivatives

Joan-Carles Fernàndez,[a,*] Laia Solé-Feu,[a] Dolors Fernández-Forner,[b] Natalia de la Figuera,[a] Pilar Forns[a] and Fernando Albericio[c]

[a]*Almirall Prodesfarma-Barcelona Science Park Unit, Barcelona Science Park, Josep Samitier 1, 08028 Barcelona, Spain*
[b]*Research Center, Almirall Prodesfarma, Cardener 68-74, 08024 Barcelona, Spain*
[c]*Barcelona Biomedical Research Institute, Barcelona Science Park, Josep Samitier 1, 08028 Barcelona, Spain*

Received 22 October 2004; revised 23 November 2004; accepted 29 November 2004

Abstract—The application of the Suzuki coupling reaction to the preparation of small combinatorial libraries using 5-bromonicotinic acid as a scaffold onto three different types of solid support (Wang, Rink, and BAL resin) is described.

The formation of carbon–carbon bonds on solid-phase[1] is a particularly useful transformation but has been slower in coming of age than other solid-phase reactions. Pd-catalyzed coupling reactions[2] are the most prevalent method for creating carbon–carbon bonds in both solution and solid-phase. The Pd-catalyzed Suzuki reaction of aryl halides with boronic acids has emerged as a powerful tool in SPOS owing to its mild reaction conditions, compatibility with most functional groups and the wide availability of boronic acids.

Our group is developing strategies for generating primary screening small libraries[3] from which pharmaceutically attractive lead compounds may arise.

The success of a solid-phase synthesis is highly dependent on both the starting solid support and linker used. The relevance of these factors to the outcome of Suzuki coupling reactions is demonstrated in this work. We have thus found that Suzuki reactions employing either Wang or amide-bound resins afford distinct results. Application of the Suzuki coupling reaction to the preparation of small combinatorial libraries on three different types of solid-support using 5-bromonicotinic acid[4] as a scaffold is discussed.

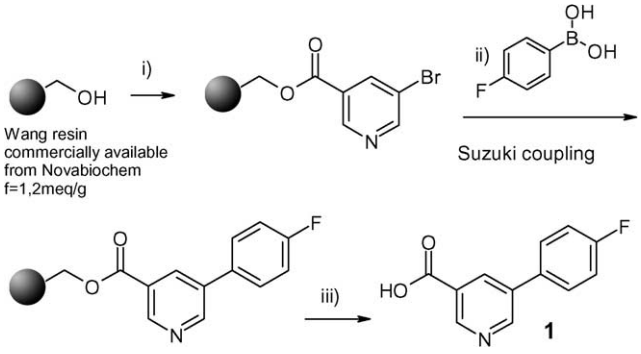
In the synthetic approach used, 5-bromonicotinic acid was first attached to a commercial Wang resin using 1,3-diisopropylcarbodiimide (DIC) and 1-hydroxy-benzotriazole (HOBt) in *N*,*N*-dimethylformamide (DMF) in the presence of a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP). In order to optimize the Suzuki reaction conditions, several bases and palladium catalysts were first studied using 3 equiv of 4-fluorophenylboronic acid (Table 1). Reactions were carried out on a 60 μmol scale, using $Pd(PPh_3)_4$ or [$PdCl_2$(dppf)]

Table 1. Representative conditions found for Suzuki Coupling on Wang Resin

Entry	Solvent	Catalyst	Base	Purity (%)	Yield (isolated) (%)
1	DMF	0.2 eq $PdCl_2$(dppf)	4 eq 2 M Na_2CO_3	75	50–60
2	DMF/H_2O (9:1)	0.2 eq $PdCl_2$(dppf)	10 eq Et_3N	80	50
3	DMF/H_2O (9:1)	5% $Pd(PPh_3)_4$	3 eq K_3PO_4	75	50
4	Toluene/EtOH (9:1)	5% $Pd(PPh_3)_4$	4 eq 2 M Na_2CO_3	50	60–80
5	DMF	5% $Pd(PPh_3)_4$	3 eq K_3PO_4	>95	>80
6	DME	5% $Pd(PPh_3)_4$	3 eq K_3PO_4	80	70

Keywords: Combinatorial chemistry; Wang resin; Rink resin; Bal resin; 5-Bromonicotinic acid; Suzuki coupling; Solid-phase organic synthesis.
* Corresponding author. Tel.: +34 934 034 705/06; fax: +34 934 037 109; e-mail: jcfernandez@pcb.ub.es

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.153



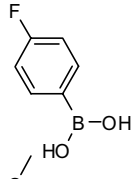
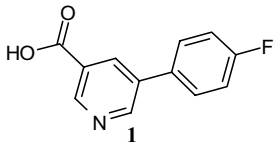
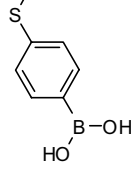
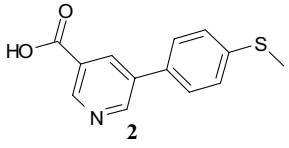
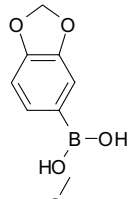
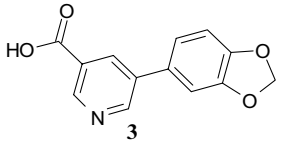
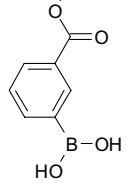
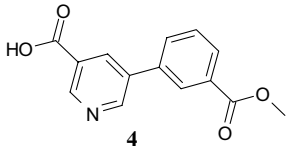
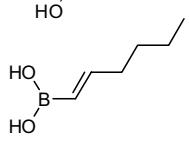
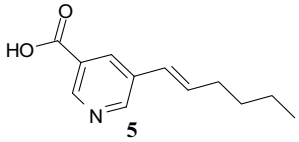
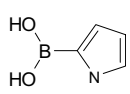
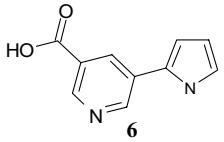
Scheme 1. Reagents and conditions: (i) 5-bromonicotinic acid, DIC, HOBt, DMAP in DMF, (ii) see Table 1 for conditions, (iii) TFA/DCM (1:1) (2 × 10 min).

as catalyst; Na_2CO_3, K_3PO_4, or Et_3N as base, and the following degassed solvents: toluene/ethanol, dimethoxyethane (DME), DMF and DMF/H_2O. Reaction mixtures were heated at 80 °C for 1 day to produce the 5-(4-fluorophenyl)-nicotinic acid **1** as its trifluoroacetate salt after cleavage with trifluoroacetic acid (TFA)/dichloromethane (DCM) (1:1) (Scheme 1). All reaction steps were monitored by ^1H NMR and mass spectrometry (MS) of cleaved resin aliquots.

In conclusion, $Pd(PPh_3)_4$ is a better catalyst than $PdCl_2(dppf)$, which contaminates the final sample. When K_3PO_4 was replaced with stronger bases, such as Na_2CO_3 or Et_3N, the observation of unreacted starting material in the crude product led to the conclusion that reaction completion requires an appropriate base strength. The presence of water in the reaction is detrimental to the isolated yield, presumably because of hydrolysis of the ester bond. Hence the use of water in the reaction system should be avoided. DMF as a solvent gave slightly better results.

A variety of 24 boronic acids were tested in Suzuki reaction[5] (representative examples are shown in Table 2) employing the optimized conditions (entry 5: $Pd(PPh_3)_4$, K_3PO_4, and DMF as solvent). 5-Substituted nicotinic

Table 2. 5-Substituted nicotinic acids prepared from Wang resin

Reagent	Product	Yield[a] (%)	Purity[b] (%)	MS[c] $[M+H]^+$
	 **1**	84	93	220
	 **2**	75	78	248
	 **3**	80	94	246
	 **4**	79	90	260
	 **5**	81	96	208
	 **6**	75	89	190

[a] Yields (%) are based on the weight of crude material and are relative to the initial loading of the resin.
[b] The purity of the crude material was estimated from analytical HPLC at $\lambda = 210$ nm.
[c] Confirmed by mass spectra (ESI).

acids were isolated in good yield (75–89%) and purity (78–96%). All products were identified by LC-MS equipped with a diode array detector (Table 2). The results illustrate the tolerance of the reaction for a broad array of boronic acids. The final conditions allowed for a wide variation in arylboronic acids; good results were obtained for neutral, electron-withdrawing, and electron-donating functionalities alike.

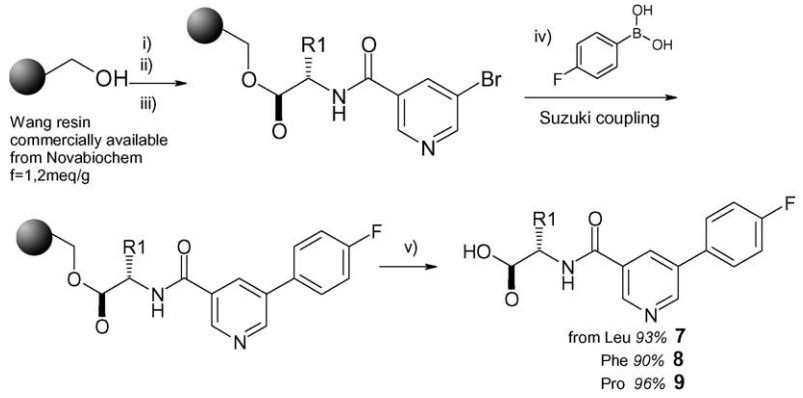
In order to introduce an additional point of diversity into the library and to check the scope and limitations of the previously optimized Suzuki reaction conditions, additional syntheses were performed. Fmoc-amino acids were loaded onto Wang resin and, after Fmoc removal, were subsequently acylated at their free amines with 5-bromonicotinic acid under standard coupling conditions.[3b]

When aminoacyl-bromonicotinic ester-bound resins were treated with 4-fluorophenylboronic acid under the aforementioned reaction conditions (Table 1, entry 5), the resulting products were obtained with high purity and in good yield (see Scheme 2). These results show that the optimized Suzuki reaction conditions also work well when an aliphatic ester is bound to the polymer support.

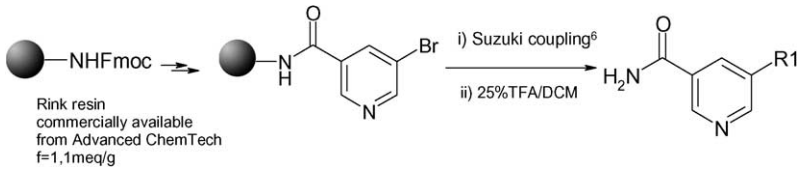
Another point of diversity has been introduced into our libraries by using Rink and BAL resins[3] as a solid support in order to prepare primary and secondary amides, respectively. Thus 5-bromonicotinic acid was incorporated onto commercial Rink and alkylamino-BAL resins via standard conditions. Application of the best Suzuki reaction conditions found for Wang-ester resin gave inferior results (44% of conversion) on Rink-amide resin. These results are in agreement with earlier findings by Lago et al., who reported that heating Suzuki coupling reactions on Rink resin at 90–95 °C in toluene/ethanol (9:1) for 24 h is required in order to achieve total conversion (see Scheme 3). Taking these findings into consideration, a small library of 24 nicotinamides was prepared in high purity (>80%).

In the BAL approach, primary amines (the second point of diversity for the case at hand) are attached to a 4-formyl-3-dimethoxyphenyloxymethyl-functionalized polystyrene resin (BAL) via reductive amination, and used to make alkylamino resins, which were subsequently acylated with 5-bromonicotinic (see Scheme 4). Although total conversion was achieved when 5-bromonicotinamide-BAL resins were reacted under the optimal Suzuki reaction conditions found for Wang resin (entry 5 in Table 1), compounds were obtained in slightly higher purity when the BAL resins were reacted under the optimized Rink conditions.[6] Using the latter reaction conditions a small library of 180 secondary nicotinamides was thus obtained[7] in good yield (75–85%) and high purity (71–96%) (representative examples are shown in Table 3).

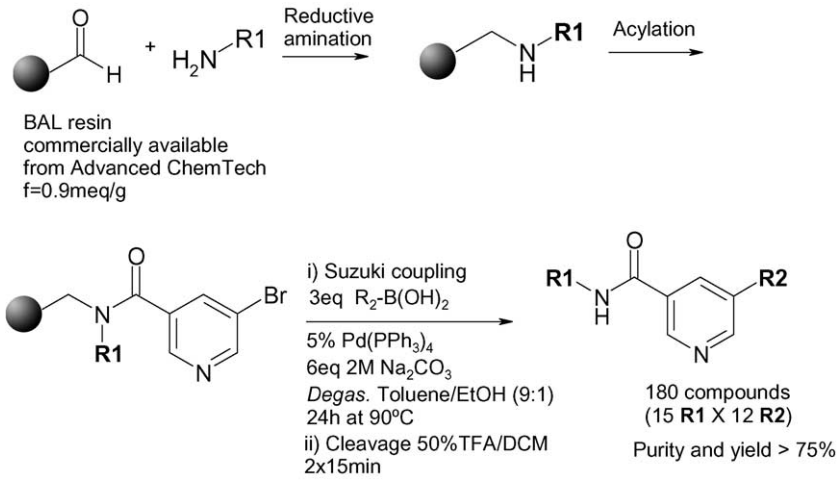
In summary, libraries of 5-substituted nicotinic acid derivatives were prepared in extremely good yield and high purity on three different solid supports (Wang, Rink, and BAL resin) via the Suzuki cross-coupling reaction. Fine tuning of the experimental conditions for each resin was required. For amide resins, the best reaction conditions employed aqueous Na_2CO_3 in toluene/EtOH (9:1) as solvent. In the case of ester-bound



Scheme 2. Reagents and conditions: (i) Fmoc-L-AA-OH, HOBt, DIC, DMAP in DCM/DMF (1:1), (ii) piperidine/DMF (4:1), (iii) 5-bromonicotinic acid, DIC, HOBt, DMAP in DMF, (iv) see Table 1, entry 5, for conditions, (v) TFA/DCM (1:1) (2 × 10 min).

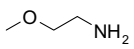
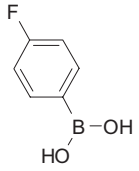
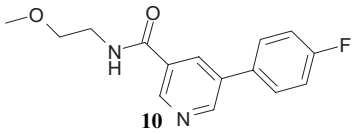
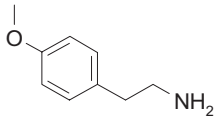
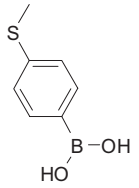
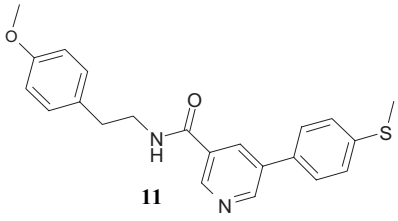
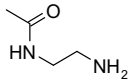
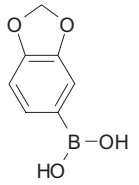
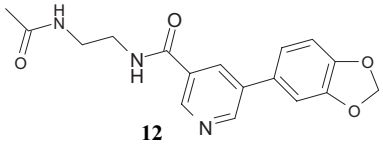
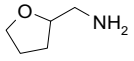
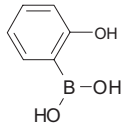
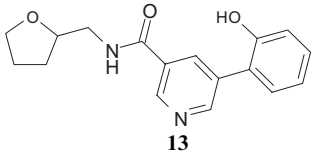


Scheme 3.



Scheme 4.

Table 3. 5-Substituted nicotinamides prepared from BAL resin

R1	R2	Product	Yield[a] (%)	Purity[b] (%)	MS[c] $[M+H]^+$
		 **10**	80	94	275
		 **11**	79	71	378
		 **12**	85	90	328
		 **13**	75	96	299

[a] Yields (%) are based on the weight of crude material and are relative to the initial loading of the resin.
[b] The purity of the crude material was estimated from analytical HPLC at $\lambda = 210$ nm.
[c] Confirmed by mass spectra (ESI).

resins, however, anhydrous conditions using K_3PO_4 in DMF were required for optimum results.

Acknowledgements

Authors thank Drs Graham Warelow and Hammish Ryder for their encouragement to perform the work.

References and notes

1. For an overview see: Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137–202, and references cited therein.
2. Bräse, S.; Kirchhoff, J. K.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885–939, and references cited therein.
3. (a) Forns, P.; Sevilla, S.; Erra, M.; Ortega, A.; Fernández, J.-C.; de la Figuera, N.; Fernández-Forner, D.; Albericio, F. *Tetrahedron Lett.* **2003**, *44*, 6907–6910; (b) Yraola, F.;

Ventura, R.; Vendrell, M.; Colombo, A.; Fernández, J.-C.; de la Figuera, N.; Fernández-Forner, D.; Royo, M.; Forns, P.; Albericio, F. *QSAR Comb. Sci.* **2004**, *23*, 145–152.

4. For examples of Pd(0) catalyzed cross-coupling of such substrate in solid-phase see: (a) Chamoin, S.; Houldsworth, S.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4175–4178; Marquais, S.; Arlt, M. *Tetrahedron Lett.* **1996**, *37*, 5491–5494; For exemples of Pd(0) catalyzed cross-coupling of such substrate in solution-phase see: (b) O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, P. E. *Org. Lett.* **2000**, *2*, 4201–4204; Doll, M. K.-H. *J. Org. Chem.* **1999**, *64*, 1372–1374; Banwell, M. G.; Cameron, J. M.; Corbett, M.; Dupuche, J. R.; Hamel, E.; Lambert, J. N.; Lin, C. M.; Mackay, M. F. *Aust. J. Chem.* **1992**, *45*, 1967–1982; Thompson, W. J.; Jones, J. H.; Lyle, P. A.; Thies, J. E. *J. Org. Chem.* **1988**, *53*, 2052–2055; Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237–5243.
5. General procedure for Suzuki reactions on Wang solid support (compounds **1**–**6**): 5-Bromonicotinic ester-bound resin (1.2 mmol/g, 60 mg) was suspended in degassed DMF (1 mL). $Pd(PPh_3)_4$ (5 mol %, 4 mg) was then added to the resin and the mixture was agitated for 10 min. K_3PO_4 (3 eq, 0.21 mmol, 42 mg) and boronic acid (3 eq, 0.21 mmol) were added to the resin, the mixture was degassed under Ar for 1 min and was subsequently shaken for 24 h at 80 °C. The resin was then filtered and washed with DMF, DCM, and MeOH (×3). Cleavage was performed using TFA/DCM (1:1) (2 × 10 min). The solvent was evaporated and the resulting residue was analyzed by HPLC/LC-MS and ^1H NMR. Compound **1**: ^1H NMR (400 MHz, DMSO-d_6) δ 9.10 (d, J = 2.0 Hz, 1H); δ 9.06 (d, J = 2.0 Hz, 1H); δ 8.47 (t, J = 2.0 Hz, 1H); δ 7.85 (dd, J = 9.0, 5.2 Hz, 2H); δ 7.35 (t, J = 9.0, 2H).
6. Lago, M. A.; Nguyen, T. T.; Bhatnagar, P. *Tetrahedron Lett.* **1998**, *39*, 3885–3888.
7. General procedure for Suzuki reactions on BAL solid support (compounds **10**–**13**): 5-Bromonicotinic amide-bound resin (0.9 mmol/g, 60 mg) was suspended in degassed toluene/EtOH (9:1) (1 mL:0.2 mL). $Pd(PPh_3)_4$ (5 mol %, 4 mg) was then added to the resin and the mixture was agitated for 10 min. 2 M Na_2CO_3 (6 equiv, 0.32 mmol, 162 μL) and boronic acid (3 equiv, 0.162 mmol) were added to the resin, the mixture was degassed under Ar for 1 min and was subsequently shaken for 24 h at 90 °C. The resin was then filtered and washed with DMF, DCM, and MeOH (×3). Cleavage was performed using TFA/DCM (1:1) (2 × 15 min). The solvent was evaporated and the resulting residue was analyzed by HPLC/LC-MS and ^1H NMR. Compound **10**: ^1H NMR (400 MHz, DMSO-d_6) δ 9.00 (d, J = 2.0 Hz, 1H); δ 8.96 (d, J = 2.0 Hz, 1H); δ 8.43 (t, J = 2.0 Hz, 1H); δ 7.85 (dd, J = 9.0, 5.2 Hz, 2H); δ 7.36 (t, J = 9.0 Hz, 2H); δ 3.47 (m, 2H); δ 3.33 (m, 2H); δ 3.27 (s, 3H).