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Solid phase palladium-catalysed C–C bond formation in the pyridine series: access to aryl and alkynyl pyridylpiperazines

Frédéric Louërat, Philippe Gros* and Yves Fort*

Synthèse Organique et Réactivité, UMR 7565, Faculté des Sciences, Université Henri Poincaré, Nancy Boulevard des Aiguillettes, BP 239, 54506 Vandoeuvre-lès-Nancy, France

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Abstract—The underdeveloped topic of solid phase C–C bond formation in pyridine series has been investigated. Stille, Negishi, Suzuki and Sonogashira cross-couplings have been performed leading to aryl and alkynyl pyridylpiperazines in acceptable to good yields.

Solid phase synthesis has become as a powerful tool for combinatorial preparation of small molecules libraries.[1] Among the hundreds of organic transformations adapted to solid phase, organometallic coupling is an attractive methodology to create C–C bonds.[2] So, considerable efforts have been devoted to solid phase development of palladium-catalysed coupling in aromatic series.[3] Curiously, only a few work deals with polymer-bound pyridines[4] due to a lack of methodologies to introduce reactive moieties onto immobilised pyridine nuclei.

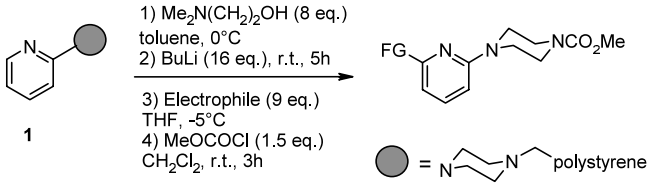
Recently, we have reported the unprecedented aminoalkoxide mediated[5] solid phase lithiation of pyridine.[6] Thus, various functionalities were introduced selectively at C-6 of polymer-bound 2-pyridylpiperazine **1**[6] and potent pharmacophores were released after cleavage from the resin (Scheme 1).

It was envisioned that such a methodology could be useful to produce reactive pyridinic precursors for coupling reactions. Herein, we report our first results on the solid phase palladium-catalysed C–C bond creation in pyridine derivatives for potential generation of libraries of aryl and alkynyl derivatives.

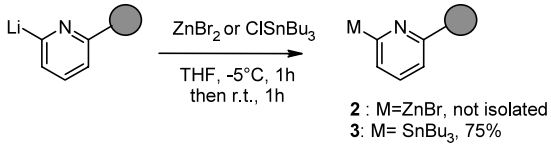
The two following routes have been explored: (i) the coupling of immobilised pyridyl organometallics. (ii) The reaction of organometallics with immobilised halogeno derivatives.

Polymer-bound organometallic species **2** and **3** were first prepared. Thus resin **1** was lithiated according to Scheme 1 and transmetallated with $ZnBr_2$ or $ClSnBu_3$·THF solutions (Scheme 2).[7]

Cleavage of **3** with methyl chloroformate (MCF) revealed a 75% stannylation yield. **2** and **3** were then subjected to palladium catalysis with $PdCl_2(PPh_3)_2$ under conditions usually used in solution (Table 1).[8] With zinc-containing resin **2**, metallation, condensation and coupling were performed in the same pot in order to avoid hydrolysis of the zinc reagent. The reactions proceeded comparably with both the immobilised organometallics giving products in acceptable yields. Unfortunately, we were unable to couple 2-bromopy-



Scheme 1. Solid phase lithiation of 2-pyridylpiperazine.



Scheme 2. Preparation of resins **2** and **3**.

* Corresponding authors. Tel.: 33 (0) 3 83 68 47 84; fax: 33 (0) 3 83 68 47 85; e-mail: philippe.gros@sor.uhp-nancy.fr

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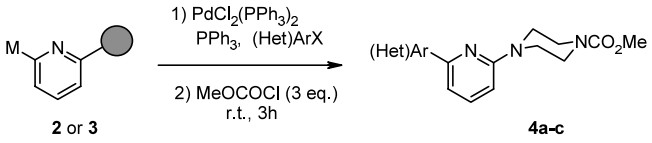
Table 1. Pd-catalysed coupling of resins **2** and **3**[a]



2 or **3** **4a-c**

Resin	(Het)ArX	(Het)Ar	Product	Coupling yield (%)[c]	Overall yield (%)[d]
2[b]	PhI	Ph	**4a**	–	40
2	2-Br-Py	2-Py	**4b**	–	Trace
3	PhBr	Ph	**4a**	45	34
3	PhI	Ph	**4a**	65	50
3	2-Br-Py	2-Py	**4b**	–	Trace

[a] Reaction conditions: Catalyst (5% based on loading of **2** and **3**), PPh_3 (20%), (Het)ArX (1.5 equiv.), DMF, reflux, 18 h.
[b] Coupling was performed in toluene–THF, reflux, 18 h.
[c] Yield after cleavage based on tin loading of **3**.
[d] Isolated yield after cleavage based on loading of **1**.

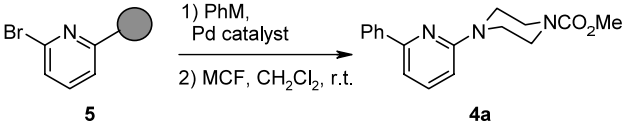
ridine which was found to undergo homocoupling in solution before reaction with the immobilised organometallics.[9]

In order to avoid such a dimerisation we turned to polymer-bound bromopyridine **5** as other potential coupling partner. **5** was prepared in 92% yield by lithiation of **1** and subsequent reaction with carbon tetrabromide[6] then subjected to Stille and Suzuki–Miyaura coupling with typical reagents (Table 2).[10]

As shown, the phenyl group was introduced in acceptable yield onto pyridine. With $PdCl_2(PPh_3)_2$ as catalyst, reduction of the C–Br bond in **5** was observed as side reaction as shown by isolation of 2-pyridylpiperazine carbamate (typically 20–30%) after cleavage from the support. As expected, no homocoupling of the polymer bound pyridine occurred. The Suzuki coupling was greatly improved by addition of CuI (10%) leading to **4a** in 71% (from **1**). Unfortunately CuI did not produce the same effect on the Stille coupling. Finally, the use of another catalyst such as Pd_2dba_3 did not give better results. The optimal Suzuki conditions were then applied to the coupling of various boronic acids leading to the expected compounds **6a–c** in acceptable yields (Table 3).

Finally, **5** was submitted to a Sonogashira coupling with terminal alkynes (Scheme 3).[11] Alkynyl pyridylpiperazines carbamates were isolated in acceptable to good overall yields (based on loading of **1**).

Table 2. Pd-catalysed coupling of resin **5**[a]

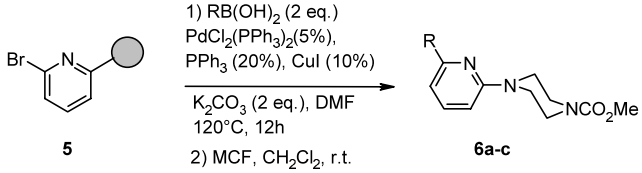


5 **4a**

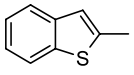
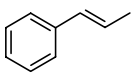
PhM	Catalyst	Additive	Conv. (%)[c]	Yield (%)[d]
$PhSnBu_3$	$PdCl_2(Ph_3)_2$[b]	–	100	58
$PhSnBu_3$	Pd_2dba_3	–	80	45
$PhB(OH)_2$	$PdCl_2(Ph_3)_2$[b]	–	100	35
$PhB(OH)_2$	$PdCl_2(Ph_3)_2$[b]	CuI	100	71
$PhB(OH)_2$	Pd_2dba_3	CuI	100	68

[a] All reactions carried out in DMF, 120°C for 12 h with PhM (1.5 equiv.), Pd° catalyst (5%), CuI (10%) when mentioned and K_2CO_3 for Suzuki couplings
[b] with PPh_3 (20%).
[c] Convertion of **5** determined by GC after cleavage.
[d] Overall isolated yield after cleavage based on loading of **1**.

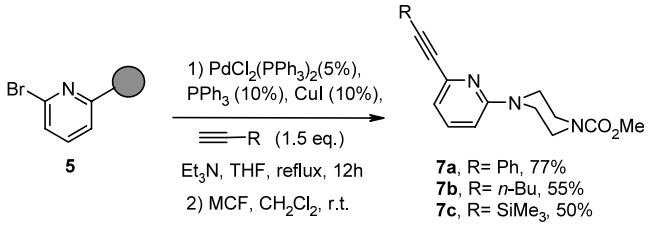
Table 3. Suzuki coupling of resin **5**[a]



5 **6a-c**

R	Product	Yield %[b]
2-naphtyl	**6a**	50
	**6b**	50
	**6c**	41

[a]All reactions carried out on 1g of **5**. [b]Overall isolated yield after cleavage based on loading of **1**.



Scheme 3. Sonogashira coupling of resin **4**.

The preparation of the immobilised silyl derivative (**7c** after cleavage) is of particular interest as a source for further introduction of diversity via 3-component Mannich condensations.[3i]

In summary we have shown that polymer-bound pyridylpiperazine can be functionalised with aryl and alkynyl groups via a lithiation-condensation-coupling sequence. The acceptable to good overall yields obtained are comparable to those found in the literature for the aromatic series. This methodology opens new perspectives in combinatorial chemistry for the preparation of diversely substituted pyridyl derivatives on a solid phase.

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7. **Procedure for preparation of 3**. 2-Dimethylaminoethanol (1.6 mL; 16 mmol) was added to resin **1** (1 g; 1.92 mmoles) preswelled in toluene (20 mL) for 15 min, under N_2. After 15 min, the mixture was cooled at −5°C and butyllithium (20 mL of a 1.6 M solution in hexanes; 32 mmoles) was added dropwise. The suspension was then stirred at –5°C for 1 h and at room temperature for 6 h. The suspension was then cooled at −5°C and treated with a solution of tributyltin chloride (4.90 mL, 18 mmoles) in THF (20 mL). The temperature as then maintained at −5°C for 1 h and allowed to warm to room temperature overnight. The tin content in **3** was then obtained as follows: **3** (1 g) was suspended in dichloromethane (10 mL) and MCF (0.8 mL; 10.4 mmoles) was added under a nitrogen stream. After 3 h of stirring at room temperature, the resin was filtered and washed with dichloromethane. Evaporation of filtrate and purification by chromatography (AcOEt/hexane) afforded the expected stannane as an oil (0.73 g, 75%): ^{1}H NMR ($CDCl_3$): δ 7.31 (t, $J=8.0$ Hz, 1H), 6.78 (d, $J=7.6$ Hz, 1H), 6.46 (d, $J=8.4$ Hz, 1H), 3.73 (s, 3H), 3.56 (m, 8H), 1.64 (q, 6H), 1.35–1.20 (m, 12H), 0.92 (t, 9H). ^{13}C NMR ($CDCl_3$): δ 171.8, 158.7, 156.1, 135.1, 123.2, 105.7, 52.7, 45.0, 43.6, 29.2, 27.9, 26.9, 13.8. Resin **2** was prepared identically to **3** except that a solution of zinc bromide (4.1 g, 18 mmoles) in THF (20 mL) was used.
8. **Procedure for Stille cross-coupling of 3**. A suspension of **3** (1 g, 1.40 mmoles), iodobenzene (0.26 mL; 2.10 mmoles), $PdCl_2(PPh_3)_2$ (49 mg; 5%), PPh_3 (73 mg; 20%) in DMF (50 mL), was refluxed under N_2 for 12 h. After cooling, the reaction mixture was filtred and washed with NH_4OH, H_2O, THF and ether. After drying, cleavage with MCF and chromatography, **4a** was obtained as a yellow gummy solid (280 mg, 50%) ^{1}H NMR ($CDCl_3$): δ 8.05 (d, $J=7.5$ Hz, 2H), 7.48 (t, $J=7.5$ Hz, 1H), 7.45–7.35 (m, 3H), 7.12 (d, $J=7.5$ Hz, 1H), 6.56 (d, $J=8.5$ Hz, 1H), 3.71 (s, 3H), 3.64 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 158.7, 159.0, 155.9, 139.6, 138.3, 128.6, 128.4, 126.7, 110.1, 105.6, 52.6, 45.1, 43.5. MS (EI) m/z (rel. int.): 297 (13, M^+), 209 (11), 195 (11), 184 (15), 183 (100), 155 (12) 154 (18), 127 (8), 59 (6).
   Procedure for one-pot Negishi cross-coupling of 2. To the above prepared suspension of **2** were added iodobenzene (0.26 mL; 2.10 mmoles 1.5 equiv.), $PdCl_2(PPh_3)_2$ (49 mg; 5%) and PPh_3 (73 mg; 20%). The suspension was then refluxed for 12 h. After cooling, the reaction mixture was filtred and washed with NH_4OH, H_2O, THF and ether. Usual cleavage and chromatography afforded **4a** (230 mg, 40%).
9. Homocoupling was demonstrated by isolation of a large amount of 2,2′-bipyridine in the filtrate.
10. **Procedure for Stille cross-coupling of 5**. A suspension of **5**[6] (1 g, 1.78 mmoles), phenyltributyltin (0.87 mL; 2.67 mmoles 1.5 equiv.), $PdCl_2(PPh_3)_2$ (62 mg; 5%), PPh_3 (94 mg; 20%) in DMF (50 mL) was refluxed under N_2 for 12 h. Usual washings, cleavage and chromatography afforded **4a** (303 mg, 58%). **Procedure for Suzuki cross-coupling of 5**. A suspension of **5**[6] (1 g, 1.78 mmoles), aryl boronic acid (2.67 mmoles 1.5 equiv.), $PdCl_2(PPh_3)_2$ (94 mg, 5%), PPh_3 (g, 20%), CuI (34 mg, 10%) and K_2CO_3 (2 g, 0.015 mmoles) in DMF (50 mL) was refluxed under N_2 for 12 hours. Usual washings, cleavage and chromatography afforded **4a** (400 mg, 71%). **6a** (0.32 g, 50%). ^{1}H

NMR ($CDCl_3$): δ 8.24 (d, $J=7.5$ Hz, 1H), 7.85 (d, $J=7.6$ Hz, 2H), 7.50 (m, 5H), 6.92 (d, $J=7.5$ Hz, 1H), 6.62 (d, $J=7.5$ Hz, 1H), 3.71 (s, 3H), 3.68 (s, 8H). ^{13}C NMR ($CDCl_3$): δ 158.6, 157.40, 139.0, 138.0, 134.0, 131.2, 128.5, 128.2, 127.2, 125.9, 125.7, 125.3, 114.9, 105.3, 52.6, 45.0, 43.5. MS (EI) m/z (rel. int.): 347 (18, M^+), 259 (8), 245 (12), 234 (17), 233 (100), 231 (7), 205 (6), 204 (21), 203 (8), 56 (5). **6b** (320 mg, 50%). ^1H NMR ($CDCl_3$): δ 7.81–7.74 (m, 3H), 7.53 (t, $J=7.5$ Hz, 1H), 7.34–7.29 (m, 2H), 7.17 (d, $J=7.4$ Hz, 1H), 6.56 (d, $J=7.4$ Hz, 1H), 3.74 (s, 3H), 3.63 (s, 8H). ^{13}C NMR ($CDCl_3$): δ 158.5, 156.1, 150.5, 148.8, 140.6, 138.3, 137.8, 124.8, 124.4, 124.0, 122.5, 120.5, 109.3, 106.1, 52.8, 44.9, 43.5. **6c** (0.25 g, 41%). ^1H NMR ($CDCl_3$): δ 7.58–7.36 (m, 7H), 7.00 (d, $J=16$ Hz, 1H), 6.72 (d, $J=7.4$ Hz, 1H), 6.54 (d, $J=7.5$ Hz, 1H), 3.74 (s, 3H), 3.62 (s, 8H). ^{13}C NMR ($CDCl_3$): δ 158.7, 156.0, 153.6, 138.2, 137.0, 131.9, 128.7, 128.5, 128.0, 127.1, 113.1, 106.2, 52.8, 45.0, 43.6.

11. **Procedure for Sonogashira coupling of 5**. A mixture of **5** (1 g, 1.78 mmoles), alkyne (2.67 mmoles 1.5 equiv.), $PdCl_2(PPh_3)_2$ (62 mg; 5%), PPh_3 (94 mg; 20%), Et_3N (5 mL; 0.035 mmoles) in THF (50 mL), was refluxed under N_2 for 12 h. Usual washings, cleavage and chromatography afforded alkynylpyridines. **7a** (470 mg, 77%). ^1H NMR ($CDCl_3$): δ 7.58 (m, 2H), 7.45 (t, $J=8.9$ Hz, 1H), 7.32 (m, 3H), 6.91 (d, $J=8.8$ Hz, 1H), 6.58 (d, $J=8.8$ Hz, 1H), 3.72 (s, 3H), 3.56 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 158.8, 155.9, 141.2, 137.6, 132.2, 128.2, 122.5, 119.1, 117.5, 106.8, 89.4, 87.8, 52.6, 44.7, 43.2. MS (EI) m/z (rel. int.): 321 (15, M^+), 219 (13), 208 (18), 207 (100), 178 (13), 58 (10), 56 (11). **7b** (320 mg, 55%). ^1H NMR ($CDCl_3$): δ 7.40 (t, $J=8.5$ Hz, 1H), 6.75 (d, $J=7.8$ Hz, 1H), 6.54 (d, $J=7.8$ Hz, 1H), 3.72 (s, 3H), 3.53 (m, 8H), 2.45 (t, $J=6.4$ Hz, 2H), 1.55 (m, 4H), 0.93 (t, $J=6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 158.8, 155.9, 141.9, 137.5, 117.2, 106.2, 89.6, 80.9, 52.7, 44.8, 43.5, 30.5, 22.1, 19.1, 13.6. MS (EI) m/z (rel. int.): 301 (13, M^+), 213 (6), 199 (10), 188 (13), 187 (100), 144 (6), 56 (10). **7c** (300 mg, 50%). ^1H NMR ($CDCl_3$): δ 7.42 (t, $J=8.2$ Hz, 1H), 6.84 (d, $J=7.6$ Hz, 1H), 6.59 (d, $J=7.6$ Hz, 1H), 3.73 (s, 3H), 3.55 (m, 8H), 0.26 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 158.7, 155.9, 140.9, 137.5, 128.6, 117.9, 107.1, 104.5, 93.1, 52.7, 44.7, 43.4. MS (EI) m/z (rel. int.): 317 (35, M^+), 316 (34), 315 (30), 229 (14), 215 (22), 202 (100), 58 (7).