Pergamon

Tetrahedron Letters 40 (1999) 4335–4338

TETRAHEDRON LETTERS

Preparation of new functionalized hydrocarbon linkers via Suzuki cross coupling reaction

Cécile Vanier, Alain Wagner and Charles Mioskowski*

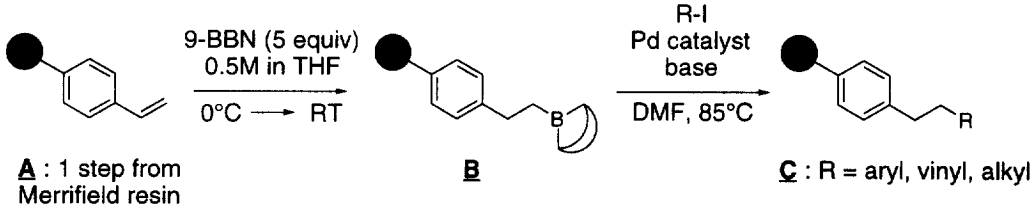
Laboratoire de synthèse bio-organique, Université Louis Pasteur de Strasbourg, UMR 7514 associée au CNRS, Faculté de Pharmacie, 74 route du Rhin - B.P. 24 - 67401 Illkirch cedex FRANCE

Received 8 March 1999; accepted 17 April 1999

Abstract: Treatment of a vinyl resin with 9-BBN affords a polymer bound alkylborane that undergoes palladium-catalyzed Suzuki cross coupling reactions with a variety of aromatic, vinylic and aliphatic halides. The mild reaction conditions are compatible with several functional groups and allow carbon-carbon bond formation at non-activated positions. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Since its introduction in 1963 by Merrifield, solid phase synthesis (SPS)[1] has become an essential tool in the drug discovery process[2]. This led chemists to face problems inherent to the use of polymeric systems: improving the resin (loading, mechanical behavior), choosing the linker, developing a chemistry to prepare original structures with adapted retrosynthetic approaches. Among these parameters, the choice of the adapted linker is one important factor in the success of SPS. First, its stability and reactivity determine the chemistry that can be carried out. Moreover, its presence highly improves the use of routine ^{13}C NMR for analysis of resin bound molecules[3]. Several linkers have already been developed, but most of them are attached to the polystyrene backbone through oxygen and/or nitrogen benzylic bonds that are labile in oxidative or reductive conditions[4] (DDQ, ozonolysis, hydrogenation). Alternative solutions[5, 6] have already demonstrated the advantages of hydrocarbon linkers.

In this paper, we describe the preparation of hydrocarbon linkers **C** bearing various functional groups. We investigated the coupling of a polymer bound homobenzylborane **B** with aryl, vinyl and alkyl iodides, using palladium catalysts under basic conditions (**Scheme 1**).



Scheme 1

* mioskow@aspirine.u-strasbg.fr

0040-4039/99/$ - see front matter © 1999 Published by Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00788-1

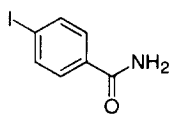
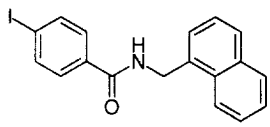
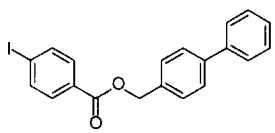
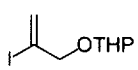
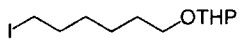
Palladium-catalyzed chemistry is one of the most powerful methods to create carbon-carbon bonds under relatively mild reaction conditions. In particular, the Suzuki cross coupling[7] is widely reported and has already been adapted to solid phase[8]. The most commonly used strategy involves the reaction of a polymer bound aryl halide with a boronic acid or an alkyl borane in solution. One drawback of this approach lies in the relatively small number of commercially available boronic acids compared to the much more widely available halides.

Our synthetic scheme involves the supported homobenzylborane **B** which was prepared by reaction of 9-BBN with the vinyl resin **A**, obtained in one step from Merrifield resin[9].

The hydroboration of resin **A** to resin **B** was shown to require 8 hours to go to completion. An already published prodedure[9] has shown, through an oxidative work up, that the reaction is almost quantitative. It is noteworthy that elemental analysis of the resins after the Suzuki coupling, have shown the absence of boron. Thus the unreacted borane has probably been converted to an ethylpolystryrene derivative which is not reacting in the following steps.

After washing off the excess of 9-BBN, the resin was used directly in the coupling reaction and all the parameters were optimized by varying the conditions: substrate, catalyst, ligand, base, temperature. The best results are summarized in **Table 1**.

Table 1: Suzuki cross coupling of polymer bound alkylborane with aryl, vinyl and alkyl halides.

Entry	Substrate (R-I)	Palladium catalyst	Ligand	Base	Yield[a] **C** (%)
1		$Pd(OAc)_2$	PPh_3	NaOH	83
2		$Pd(OAc)_2$	PPh_3	NaOH	85
3		$Pd(OAc)_2$	$S=PPh_3$	Et_3N	68
4		$PdCl_2(dppf)$	-	K_2CO_3	60
5		$PdCl_2(dppf)$	-	K_2CO_3	55

[a]: Yields of **C** were calculated as described in note 10.

As expected the reaction conditions were shown to be compatible with several functional groups (amides, esters, protected alcohols) and the corresponding hydrocarbon linkers **C** were

formed with good yields (55 % to 85 %). In general, we observed that the reactions took place only above a temperature of 80°C and required at least 14 hours. Acetonitrile or DMF appeared to be good solvents for the coupling reaction. Iodo derivatives were shown to be more reactive than their bromo counterparts.

With aryl halides (entries **1**, **2**, and **3**) the best catalytic efficiencies were obtained with the simplest and less expensive palladium catalyst ($Pd(OAc)_2$) in the presence of ligands such as triphenylphosphine or triphenylphosphine sulfide. Under the optimized conditions, good yields (up to 85 %) are obtained with aromatic amides (entries **1** and **2**). In the case of the 4-iodobenzoate derivative (entry **3**), the use of triphenylphosphine sulfide instead of triphenylphosphine improved the yields from 56 % to 68 %. The couplings of non aromatic halides with the same catalytic system were found to proceed at a poor rate (<10%) whereas $Pd(dppf)Cl_2$ was found much more efficient, allowing yields up to 60% (entries **4** and **5**). Surprisingly $Pd(PPh_3)_4$ was found inefficient under our conditions: no reaction occurred with aliphatic halides, and modest yields were obtained with aryl halides.

The best base/catalyst tunings were found to be K_2CO_3 in association with $Pd(dppf)Cl_2$ and NaOH with $Pd(OAc)_2$, both in the presence of a phase transfer agent (Triton® B). To achieve the coupling with the 4-iodobenzoate derivative (entry **3**) without hydrolysis of the ester function, Et_3N was used instead of NaOH. No reaction occurred in the absence of base.

Thus we have demonstrated that a polymer bound alkylborane is a versatile precursor for the preparation of many functionalized resins. The palladium-catalyzed coupling reactions can be achieved with a good reproducibility and reliability using a range of substrates. It is noteworthy that it was possible to prepare a chemically stable aliphatic linker by carbon-carbon bond formation, through the coupling of a ω-functionalized alkyl iodide. Furthermore the procedure described herein can not only be applied for the preparation of linkers but might be extended to introduce diversity on polymer bound scaffolds bearing a double bond.

Hydroboration of the vinyl resin A:

A dry 10 mL flask was charged under argon with 200 mg of the vinyl resin **A** (1.27 meq/g). The resin was cooled down to 0 °C and 9-BBN (2.5 mL of a 0.5 M solution in THF, 5 eq) was added. The resulting suspension was swirled for 30 min at 0°C and allowed to react at RT for another 8 h. It was then quickly filtered, washed with anhydrous THF and finally dried under vacuum.

Typical procedure for the coupling reactions:

A conical flask was charged, under argon, with the palladium catalyst (0.3 eq), the ligand (0.9 eq), the iodide (4 eq), the 9-BBN derivatized resin **B**, the base (3 eq), DMF and Triton® B (1.5 eq) if required. The resulting suspension was de-gassed by gently bubbling argon and the flask was sealed. The reaction was carried out at 85 °C for 14 hours. After cooling, the resin **C** was filtered and washed successively with DMF (2x5 mL), CH_2Cl_2/AcOH 1:1 (5 mL), then 5 times alternatively with CH_2Cl_2 (5 mL) and MeOH (5 mL) and finally dried under vacuum.

FTIR microspectroscopy:

All spectra were collected on a Perkin Elmer Spectrum 2000 spectrophotometer. The optical bench is coupled with a Perkin Elmer Autoimage IR microscope and data were recorded in the transmission mode. A few randomly chosen resin beads were flattened and transferred to a KBr window. Using the view mode, the incident radiation was focused on a single resin bead. Sixty-four scans were averaged.

The spectra were normalized making the areas of the resin band at 1944 cm^{-1} of equal value in each spectrum[11,12]. Areas of IR carbonyl bands of the amide and the acetylated hydroxy resins (respectively at 1764 and 1735 cm^{-1}) were then compared to standard resins.

Acknowledgments:

We thank Rhône-Poulenc Rorer for financial support through a BDI grant to Cécile Vanier, and Franco Manfré for helpful discussions.

References and notes:

1 R. B. Merrifield: *J. Am. Chem. Soc.* **1963**, *85*, 2149.
For reviews, see: (a) S. J. Shuttleworth, S. M. Allin, P. K. Sharma: *Synthesis*, **1997**, 1217-1239. (b) F. Balkenhol, C. von dem Busshce-Hünnenfield, A. Lansky, C. Zechel: *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288-2337. (c) L. A. Thompson, J. A. Ellman: *Chem. Rev.* **1996**, 555-600.

2 P. H. H. Hermkens, H. C. J. Ottenheijm, D. Rees: *Tetrahedron* **1996**, *52*, 4527.

3 F. Lorgé, A. Wagner, C. Mioskowski: *J. Comb. Chem.* **1999**, *1*, 25-27.

4 T. R. Deegan, O.W. Gooding, J. A. Porco Jr.: *Tetrahedron Lett.* **1997**, *38*, 4973-4976.

5 S. Kobayashi, M. Moriwaki: *Tetrahedron Lett.* **1997**, *38*, 4251-4254.

6 Y. Hu, J. A. Porco Jr., J. W. Labadie, O. W. Gooding: *J. Org. Chem.* **1998**, *63*, 4518-4521.

7 A. Suzuki: *Pure. Appl. Chem.* **1985**, *57*, 1749-1758.

8 (a) B. J. Backes, J. A. Ellman: *J. Am. Chem. Soc.* **1994**, *116*, 11171-11172. (b) J. W. Guiles, S. G. Johnson, W. V. Murray: *J. Org. Chem.* **1996**, *61*, 5169-5171. (c) R. Frenette, R. W. Friesen: *Tetrahedron Lett.* **1994**, *35*, 9177-9180. (d) B. Ruhland, A. Bombrun, M. A. Gallop, *J. Org. Chem.* **1997**, *62*, 7820-7826. (e) S. D. Brown, R. W. Armonstrong: *J. Org. Chem.* **1997**, *62*, 7076-7077.

9 C. Sylvain, A. Wagner, C. Mioskowski: *Tetrahedron Lett.* **1998**, *39*, 9679-9680.

10 Yields of **C** have been determined according to different methods:
Amide resins (entries **1** and **2**): The IR carbonyl bands (1764 cm^{-1}) have been integrated and compared to commercially available resins as references.
Ester resin (entry **3**): The yield has been measured by weighting out the 4-biphenylmethanol released after transesterification of **C** with MeONa in MeOH/THF.
Protected hydroxy resins (entries **4** and **5**): The THP protecting group has been removed by treatment with pTsOH in dioxan/H_2O 8:2 (40°C, 4 hours) and the resulting free alcohol has then been acetylated by reaction with acetyl chloride in dichloromethane (RT, 12 hours).
The IR carbonyl band (1735 cm^{-1}) has been integrated and compared to references to give the yield of the coupling.

11 B. Yang, J. B. Fell, G. Kumaravel: *J. Org. Chem.* **1996**, *61*, 7467-7472.

12 B. Yang, G. Kumaravel, H. Anjara, A. Wu, R. C. Petter, C. F. Jewell Jr., J. R. Wareing: *J. Org. Chem.* **1995**, *60*, 5736-5738.