Pergamon

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Aryl-Aryl Cross Coupling on a Solid Support using Zinc Organic Reagents and Palladium Catalysis

Sophie Marquais and Michael Arlt

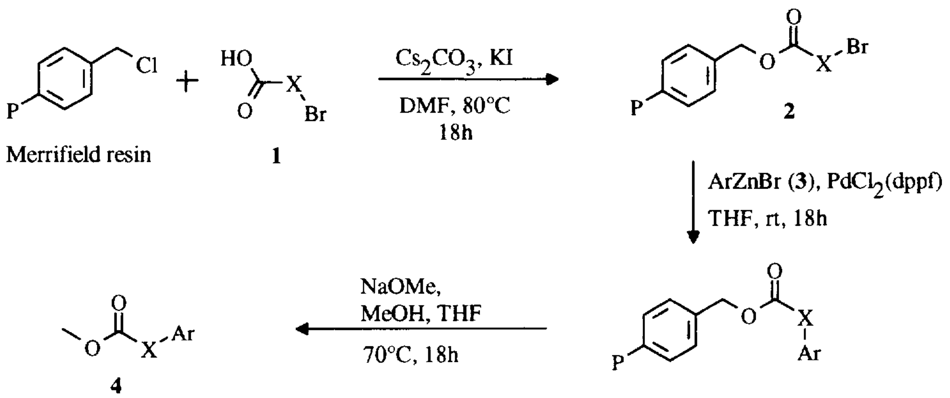
Merck KGaA, Medicinal Chemistry Research Laboratories, Frankfurter Strasse 250, D-64271 Darmstadt, Germany,
E-mail : m_arlt@merck.de

Abstract: Aryl zinc bromides undergo palladium catalyzed coupling reactions to aryl bromides which are bound to a polystyrene resin via an ester linkage. Liberation of the biaryl carboxylic ester was achieved by transesterification. Copyright © 1996 Elsevier Science Ltd

Combinatorial chemistry has recently received much interest[1]. Together with the developments in solid phase synthesis[2] this methodology offers the possibility of producing huge numbers of structures in automated procedures. For solid phase synthesis of peptides and nucleotides well established methods are employed in laboratories all over the world. However, for the synthesis of small organic molecules there is still a great need for widely applicable procedures.

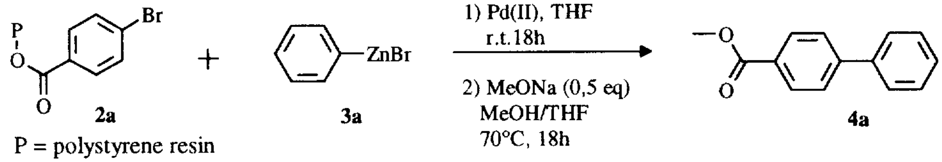
The biaryl moiety is part of many pharmacological active compounds, e. g. the angiotensin antagonists[3]. Recently, Frenette and Friesen[4] published a method for the synthesis of biphenyls via Suzuki reaction of a phenyl boronic acid with a polymer bound iodo or bromo benzoic acid. However, not many phenyl boronic acids are commercially available and they are mostly synthesized form the corresponding phenyl bromides via arylmetal species, like Grignard reagents or phenyl lithium compounds. On the other hand it is known that aryl zinc reagents can be employed in the synthesis of biphenyls and that they can be obtained via transmetallation of lithium or magnesium organic reagents[5]. Zinc reagents are especially suited for this purpose since they leave many functional groups unaffected.

In this paper we report the use of zinc aryl halogenides to form biaryls form polymerbound aromatic bromo acids. The resin bound arylcarboxylic acids **2** were obtained by reaction of acid **1** with a commercially available Merrifield resin analogously to the conditions given in the literature[4]. All resins **2** produced in this manner were loaded with 1.4 mmol/g (determined for each batch by cleavage directly after the coupling).



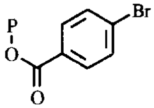
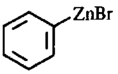
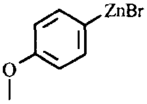
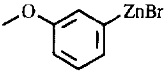
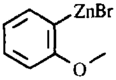
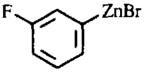
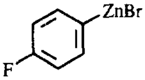
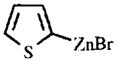
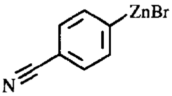
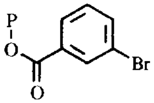
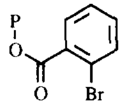
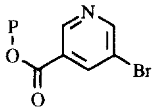
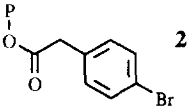
To investigate the applicability of several palladium catalysts the following system was chosen as a model: coupling of phenyl zinc bromide (**3a**, 2 equivalents, prepared by transmetallation from the corresponding Grignard reagent with $ZnBr_2$) with polymer bound 4-bromobenzoic acid (**2a**), Pd(II) catalyst (1%), THF, ambient temperature, 18h. The products were cleaved from the resin by transesterefication with 0.5 eq NaOMe in MeOH-THF 1:4, 70°C, 18h. After cleavage the crude products were investigated by HPLC. As can be seen in Table 1 all applied palladium catalysts were effective with $PdCl_2[P(o\text{-}tol)_3]$ and $PdCl_2$(dppf) being slightly superior (high yield and purity, entry 1 and 4, respectively).

Table 1. Use of Different Catalysts in the Synthesis of 4a



Entry	Pd^{II}	Yield (%)	HPLC (%)
1	$PdCl_2$(dppf)	76	98
2	$Pd(PPh_3)_4$	72	94
3	$PdCl_2(PPh_3)_2$	85	89
4	$PdCl_2(P(o\text{-}Tolyl)_3)_2$	79	96

Table 2. Cross Coupling of Aryl Zinc Reagents to Polymer Bound Bromo Aryl Compounds

Entry	Polymer Bound Acid 2[a]		Aryl Zinc Bromide 3		Biaryl 4	Yield (%)
1		2a		3a	4a	76
2		2a		3b	4b	82
3		2a		3c	4c	80
4		2a		3d	4d	75
5		2a		3e	4e	84
6		2a		3f	4f	84
7		2a		3g	4g	85
8		2a		3h	4h	61
9		2b		3e	4i	75
10		2c		3e	4j	71
11		2d		3e	4k	55[b]
12		2e		3e	4l	60[b]

[a] P = polystyrene resin; [b] contains about 15% of the corresponding acid

Next, several aryl zinc reagents were tested in the biaryl synthesis. The results in Table 2 show that methoxy substituted phenyl zinc reagents **3b-d** give good yields (entries 2-4). In the case of the fluorinated reagents **3e**, **f**[6] 5 eq were used due to their lower reactivity (entries 5 and 6). Thiophene-2-zinc bromide **3g** was prepared by orthometallation of thiophene and subsequent transmetallation with $ZnBr_2$. Its performance in the coupling reaction was good (yield 85%, entry 7). In this case, transmetallation of aryl lithium reagents is very advantageous because they can be made with reactive functional groups unaffected at low temperatures[7]. Thus, p-bromobenzonitrile was lithiated at -78°C, transmetallated with $ZnBr_2$ and treated with **2a**. After cleavage from the resin the product was obtained in 61% yield. In order to test the applicability of other bromo aromatic compounds resins **2b-e** were synthesized. The zinc reagent **3e** was treated with resins **2b-e** to yield the biaryls **4i-l**, respectively (entries 9-12). It is interesting that under standard cleavage conditions mixtures of the corresponding acids and methyl esters of **4k** and **4l** were obtained. In addition, the cleavage yield was only moderate after 18h. However, the crude products were generally of greater than 85% purity (HPLC).

In summary, we have found an efficient method to perform aryl-aryl couplings on a solid support which is an alternative to the Suzuki reaction, especially when the desired boronic acids are not easily accessible.

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6. To our best knowledge the corresponding boronic acid of reagent **3e** is not commercially available.
   Typical Procedure: 5 mmol of 3-fluorophenylmagnesium bromide (prepared from 875 mg of 3-fluorobromobenzene and 122 mg magnesium in 5 ml of THF) were transmetallated by adding a solution of 1.13 g (5 mmol) of dried $ZnBr_2$ in 5 ml of THF at 0°C. After stirring for 15 min at 0 °C 500 mg of resin **2a** (loading 1.4 mmol/g) and 15 mg of $PdCl_2$(dppf) were added. The mixture was stirred at ambient temperature for 18h. The polymer was then filtered on a fritted reservoir and washed successively with THF/water (1/1), THF, MeOH and ether. The resin was cleaved in a mixture of THF (4 ml) and MeOH (1 ml) in the presence of 30 mg of sodium methylate at 70°C overnight. After cooling, the resin was filtered and washed with THF, THF/water and ether. The product was then extracted with ethyl acetate. Evaporation of the solvent yielded 135 mg (84%, based on **2a**) of methyl 4-(3-fluorophenyl)benzoate **4e** (purity > 98% by HPLC).
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