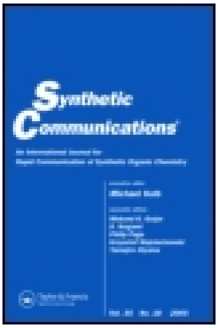

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THE SUZUKI REACTION UNDER SOLVENT-FREE CONDITIONS

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ABSTRACT: The coupling reaction of diverse arylhalogenids with phenylboronic acid under solvent-free conditions has been performed using a palladium catalyst. The order of reactivity was complementary to the normal Suzuki reaction.

There is currently a great deal of interest in performing chemical reactions under solvent-free conditions since there are both financial and environmental benefits when this can be accomplished.[1,2]

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One problem when performing reactions with solid starting materials is the mixing of the reactants so they can come into contact with each other. Another is the difficulty of uniform and controlled heating of large amounts of powdery materials. In a previously published synthesis of binaphthol both these hurdles were overcome by a ball-milling procedure, in which the milling gives very thorough mixing and at the same time a moderate heating.[3] The success in that case led us to investigate the Suzuki reaction under ball-milling conditions.

One factor that is necessary to take into consideration when designing procedures to be used in a ball-mill is the degree of stickiness of the mixture. It is not possible to mill very soft or waxy substances in a productive way since they stick to the walls of the milling chamber. We found addition of sodium chloride to the reaction mixures to be an efficient way to make them sufficiently powdery. Sodium chloride has the following favorable characteristics that influenced our choice: hard and brittle crystals, chemical inertness, good water solubility, low toxicity and low price.

In Table 1 are summarized the results of Suzuki couplings of phenylboronic acid (1.5 eq.) with 2-bromonaphthalene. Potassium carbonate gave the best yield of coupling product so we chose to use it as the base for the rest of the investigation. Twice the amount of potassium carbonate (6 eq.) did not improve the reaction. Homocoupling of the arylboronic acid was a significant side

Table 1. Effect of different bases on the relative concentrations of starting material (2-bromonaphthalene), product (2-phenylnaphtalene) and byproduct (biphenyl) after 30 minutes reaction time (based on GC-MS). Conditions A in experimental part.

Base (3 eq.)	2-Bromonaphthalene (%)	2-Phenylnaphthalene (%)	Biphenyl (%)
Cs_2CO_3	57	25	18
CsF	61	22	17
Na_2CO_3	44	37	19
K_2CO_3	19	53	28
K_3PO_4	39	38	23
KOH	50	32	18
KOEt	42	45	13
KOtBu	38	31	31
K_2CO_3, 6 eq.	60	21	19

reaction for all the examples in Table 1, we subsequently used two equivalents of phenylboronic acid to avoid this as a limiting factor.

In Tables 2 and 3 are summarized the yields of the reactions of phenylboronic acid with a series of aryl halides. The entries are arranged after falling yields of product. It can be seen from this table that aryl bromides that would be expected to be reactive under ordinary Suzuki conditions (e.g. entries **24-27**) in solution are generally poor substrates whereas the electron rich bromides such as 3-bromoanisole (entry **2**) or 3-bromoaniline (entry **4**), which are not as good substrates in the solution reaction, generally give high yields. This is complementary to the normal scope of the Suzuki reaction. It seems that when the aryl bromide has a functionality that is expected to coordinate to palladium,

Table 2. Isolated yields for the reactions between phenyl boronic acid and various substrates. Method A, experimental part.

Entry	Reaction time (min)	Substrate	Product	Yield (%)	mp (°C)
1	40	2-Bromo-naphthalene	2-Phenyl-naphthalene	96	101 103.5[4]
2	40	3-Bromo-anisole	3-Phenylanisole	93	oil[5]
3	40	5-Bromo-1,3-benzodioxole	5-Phenyl-1,3-benzodioxole	91	oil[6]
4	40	3-Bromoaniline	3-Amino-biphenyl	89	oil lit. 30[7]
5	40	3-Chlorobromo-benzene	3-Chloro biphenyl	84	oil[8]
6	40	4-Bromo-benzotrifluoride	4-Phenyl-benzotrifluoride	82	65-66 lit. 64-66[9]

the yields become very poor (e.g. entries **18**, **21**, **22**, **24**, **25**, **28**, **30**) but otherwise both electron-donating and moderately electron-withdrawing substituents are equally acceptable (however, no nitro groups are allowed).

The small difference in yields between entries **9** and **10** show that bromine and iodine are both useful as leaving groups in this reaction.

The catalyst we used for this reaction was tetrakis(triphenylphosphine) palladium(0). An experiment was also performed with bis(triphenylphosphine)palladium dichloride but then the product of homocoupling, biphenyl,

Table 3. Yields and identity for the reactions between phenylboronic acid and various substrates based on GC-MS (cross-coupling product / (cross-coupling product + arylhalide)). Method B, experimental part.

Entry	Reaction time	Substrate	Product	Yield (%)
7	30	4-Bromo-*N,N*-dimethylaniline	4-*N,N*-Dimethylaminobiphenyl	50
8	60	3-Bromoquinoline	3-Phenylquinoline	46
9	40	4-Bromoanisole	4-Methoxybiphenyl	41
10	40	4-Iodoanisole	4-Methoxybiphenyl	34
11	40	2-Bromo-6-nitrotoluene	2-Nitro-6-phenyltoluene	27
12	30	3-Bromobenzaldehyde	3-Phenylbenzaldehyde	24
13	30	4-Bromoisoquinoline	4-Phenylisoquinoline	20
14	30	3-Bromobenzonitrile	3-Phenylbenzonitrile	12
15	45	4′-Bromoacetophenone	4-Acetylbiphenyl	11
16	30	3′-Bromoacetophenone	3-Acetylbiphenyl	10
17	30	3-Bromo-4-nitroanisole	4-Nitro-3-phenylanisole	10
18	30	2-Bromobenzonitrile	2-Phenylbenzonitrile	5
19	30	2-Bromobenzaldehyde	2-Phenylbenzaldehyde	4
20	30	2-Bromo-3-nitrotoluene	3-Nitro-2-phenyltoluene	4
21	30	4-Bromobenzaldehyde	4-Phenylbenzaldehyde	2
22	30	5-Bromopyrimidine	5-Phenylpyrimidine	2
23	30	5-Bromoindole	5-Phenylindole	1
24	30	3-Bromopyridine	3-Phenylpyridine	1
25	30	4-Bromobenzonitrile	4-Phenylbenzonitrile	0
26	30	2-Bromonitrobenzene	2-Phenylnitrobenzene	0
27	30	4-Iodonitrobenzene	4-Phenylnitrobenzene	0
28	40	4′-Bromoacetanilide	4′-Phenylacetanilide	0
29	30	4-Bromophenol	4-Phenylphenol	0
30	30	4-Bromopyridine, hydrochloride	4-Phenylpyridine	0

was found to be the main product. No attempts were made to keep air out of the reaction mixture.

Experimental

The NMR spectrum was recorded on a Bruker AM 500 MHz spectrometer with $CDCl_3$ as the solvent and the chemical shifts are referenced to TMS. The mass spectrum was obtained on a JEOL JMS AX-505W double focusing mass spectrometer. The melting points was determined with a Griffin melting point apparatus. The ball milling was performed in a Fritsch Planetary Micro Mill Pulverisette, operated at maximum setting.

Method A

A mixture of arylhalide (4.8 mmol), phenylboronic acid (1.18 g, 9.7 mmol), potassium carbonate (2.0 g, 14.5 mmol), tetrakis(triphenylphosphine)-palladium(0) (0.29 g, 5 mol %) and sodium chloride (10 g) was ball-milled for the specified time (see table 2). The mixture was dissolved and partitioned between ethyl acetate and water. The organic phase was dried over $MgSO_4$ and taken to dryness *in vacuo*. Purification by column chromatography on silica gave the phenylaryl compound.

2-Phenylnaphthalene (1)

^{1}H-NMR: δ 8.75 (s, 1H), 7.95 (dd, J = 7.7 / 7.7, 2H), 7.90 (d, J = 7.4, 1H), 7.78

(dd, J = 7.4 / 1.7, 1H), 7.77 (d, J = 7.7, 2H), 7.55 - 7.48 (m, 4H), 7.41 (dd, J = 7.7 / 7.7, 1H). GC-MS (EI): m / e = 204 (M^+).

3-Phenylanisole (2)

^{1}H-NMR: δ 7.49 (d, J = 7.2, 2H), 7.34 (dd, J = 7.2 / 7.2, 2H), 7.23 – 7.29 (m, 2H), 7.08 (d, J = 7.0, 1H), 7.03 (d, J = 2.1, 1H), 6.80 (dd, J = 7.2 / 1.7, 1H), 3.80 (s, 3H). GC-MS (EI): m / e = 184 (M^+).

5-Phenyl-1,3-benzodioxole (3)

^{1}H-NMR: δ 7.44 (d, J = 7.0, 2H), 7.33 (dd, J = 7.2 / 7.0), 2H), 7.24 (d, J = 7.2 / 7.2, 1H), 7.00 (s, 1H), 6.99 (dd, J = 7.2 / 1.7, 1H), 6.81 (d, J = 7.2, 1H) 5.93 (s, 2H). GC-MS (EI): m / e = 198 (M^+).

3-Aminobiphenyl (4)

^{1}H-NMR: δ 7.49 (d, J = 7.0, 2H), 7.35 (dd, J = 7.0 / 7.0), 2H), 7.26 (dd, J = 7.0 / 7.0, 1H), 7.15 (dd, J = 7.6 / 7.6, 1H), 6.93 (d, J = 7.6, 1H), 6.85 (s, 1H), 6.63 (d, J = 7.6, 1H), 3.87 (S, 2H). GC-MS (EI): m / e = 169 (M^+).

3-Chlorobiphenyl (5)

^{1}H-NMR: δ 7.69 (m, 1H), 7.68 (d, J = 8.1, 2H), 7.58 (d, J = 8.5, 1H), 7.57 (dd, J = 8.1 / 8.1, 2H), 7.51 - 7.46 (m, 2H), 7.44 (d, J = 8.5, 1H). GC-MS (EI): m / e = 188 (M^+).

4-Phenylbenzotrifluoride (6)

^{1}H-NMR: δ 7.73 (s, 4H), 7.63 (d, J = 7.7, 2H), 7.51 (dd, J = 7.7 / 7.7, 2H), 7.44 (dd, J=7.7 / 7.7, 1H) GC-MS (EI): m / e = 222 (M^+).

Method B

A mixture of the arylhalide (4.8 mmol), phenylboronic acid (1.18 g, 9.7 mmol), potassium carbonate (2.0 g, 14.5 mmol), tetrakis(triphenylphosphine)-palladium(0) (0.29 g, 5 mol %) and sodium chloride (10 g) was ball-milled for the specified time (see table 3). The mixture was dissolved and partitioned between ethyl acetate and water. The organic phase was analyzed by GC-MS.

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