

Suzuki–Miyaura Reaction of 4-Silyl-bromobenzenes with Phenylboronic Acid under Thermal and Microwave Conditions

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Abstract: The coupling reaction of phenylboronic acid with 4-silyl-bromobenzenes incorporating an ionic liquid support or its neutral analogue at 80 °C in DMF/H₂O in the presence of Pd(PPh₃)₄ and Na₂CO₃ takes place much faster and more efficiently under microwave irradiation than under traditional heating. It is an attractive method to carry out the generally slow Suzuki–Miyaura reactions under microwave conditions.

Keywords: Suzuki–miyaura reaction, 4-silyl substituted bromobenzenes, imidazolyl derivative, imidazolium chloride derivative, microwave.

INTRODUCTION

These days the palladium-catalyzed cross coupling reactions of aryl halogenides and organoboron compounds become a common approach in synthetic organic chemistry [1-3]. In these and other papers several types of reaction conditions were investigated to optimize yields and purities. Utilizations on solid or liquid support were also described in the literature mainly for combinatorial approaches [4-6]. Ionic liquids were also applied as the reaction medium [7,8] and efforts were made to accelerate the C–C coupling by microwave (MW) irradiation [8]. MW irradiation serves mainly as a source of heating through the appropriate solvents, especially ionic liquids. However, more localized effects that can be expected e.g. in the case of ionic liquid supports have not been investigated. In this report, direct comparison between traditional and MW-assisted heating is described for the case of an ionic liquid supported bromobenzene and a neutral analogue. The role of a special ionic liquid supported component is not limited to its beneficial effect during the work-up procedure (e.g. easy separation), but it also increases the efficiency and speed of reactions in case of MW irradiation.

RESULTS AND DISCUSSION

Recently *Bonnette* and co-workers reported the first silylated traceless ionic liquid support, which allowed the Suzuki reaction on its halogeno benzene moiety linked to an imidazolium salt by a methylene-dimethylsilyl group [9]. Aiming at the synthesis of (4-bromophenyl)benzene, the *para*-dibromobenzene did not seem to be a suitable starting

material as had two reactive centers. We decided to utilize the Suzuki–Miyaura reaction based on the variation of the above approach. We wished to use 4-trimethylsilyl-bromobenzene derivatives as masked reagents, as on treatment with bromine, their silyl group can be replaced by a bromo atom (see later). Moreover, considering that the Suzuki–Miyaura couplings, in most cases, request a prolonged reaction time, we planned to apply a special silyl group incorporating a polar moiety, such as an imidazole ring to benefit from it during the MW irradiation. We also planned to study the effect of an imidazolium unit in the silyl substituent.

The syntheses of the suitable starting materials are shown in Figs (1 and 2).

The key intermediate (4-bromophenyl)-chloromethyl-dimethylsilane (1) was prepared from *para*-dibromobenzene *via* metalation with butyl lithium and by the reaction of the intermediate, formed chloromethyl-dimethylsilyl chloride [10,11]. Chloromethylsilyl derivative 1 was then reacted with imidazole in the presence of one equivalent of triethylamine at 120 °C under MW in the absence of any solvent to give imidazolymethylsilyl derivative (2). The quaternization of methylimidazole with chloromethylsilyl derivative 1 was accomplished thermally, again in the absence of solvent to afford silyl functionalized imidazolium chloride 3 quantitatively [9].

The Suzuki–Miyaura reactions of aryl bromides 2 and 3 with phenylboronic acid in the presence of tetra(triphenylphosphino) palladium in DMF – water 9:1 were first carried out using 5 equivalents of triethylamine as the base. The coupling reactions were, however, slow at 80 °C (the completion required 17.5 h) and ca. 50% of by-products were formed in both cases as was observed by GC-MS analysis that followed the desilylation of intermediates 4 and 6 by treatment with bromine [9] (Figs (3 and 4), Table 1/entries 1

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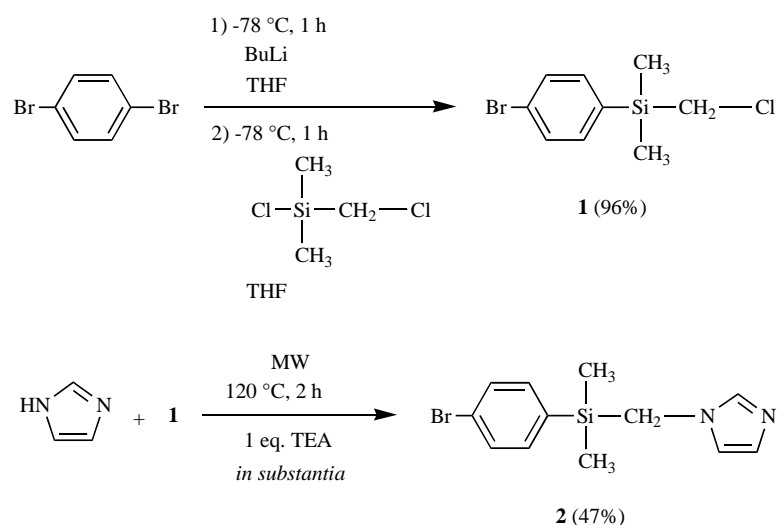


Fig. (1). Synthesis of the silyl-substituted aryl bromide **2**.

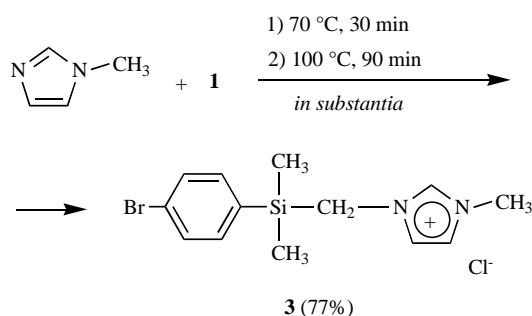


Fig. (2). Synthesis of the aryl bromide with ionic liquid support (**3**).

and **2**). A major by-product was 2,4,6-tribromophenol that may have formed in two steps. Hydrolytic cleavage of **2** and **3** leads to 4-bromophenol, whose bromination affords the tribromo derivative. The other by-product, biphenyl may be the result of the spontaneous C–Si bond fission followed the Suzuki–Miyaura reaction.

In case of 4-silyl-bromobenzene **2**, the use of 1.5 equivalent of Na₂CO₃ instead of triethylamine led to a higher proportion of product **5**. At the same time, using Na₂CO₃ less

tribromophenol (8%) and more biphenyl (33%) was formed as compared to the case applying triethylamine (Table 1/entries 3 and 1). Using starting material **3**, the product composition was independent of the base used (the ratio of **5**, tribromophenol and biphenyl was ca. 39:34:20 (Table 1/entries 4 and 2).

Better results were expected when carrying out the Suzuki–Miyaura reaction under MW conditions. The couplings of **2** and **3** with phenylboronic acid carried out as above, but

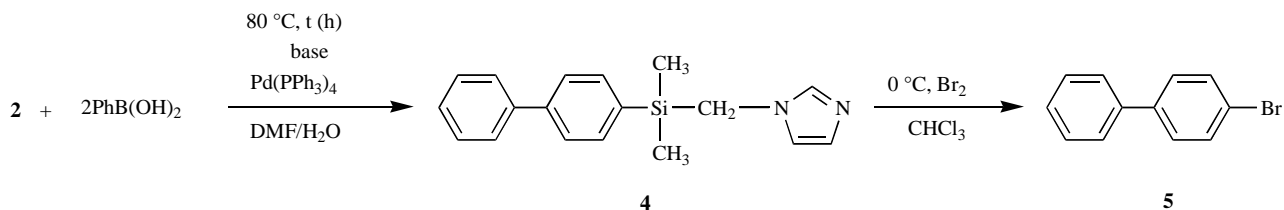


Fig. (3). Suzuki–Miyaura coupling using phenylboronic acid and an aryl bromide incorporating an imidazole moiety (**2**).

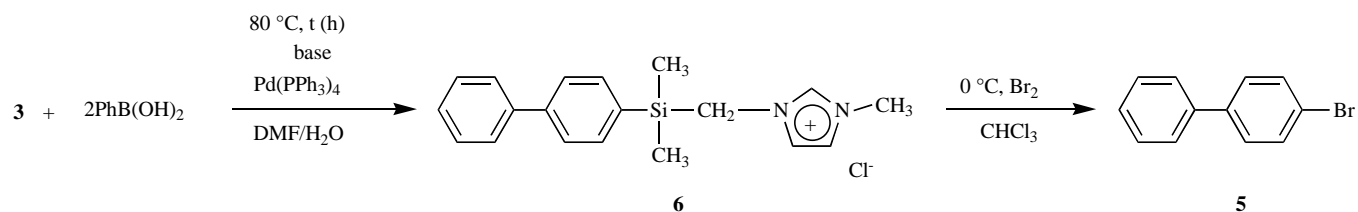


Fig. (4). Suzuki–Miyaura coupling using phenylboronic acid and an aryl bromide incorporating an ionic liquid support (**3**).

Table 1. Product Composition of the Suzuki–Miyaura Reaction Carried out Under Different Conditions at 80 °C

Heating	Starting material	Base	t	5 (%)	2,4,6-Tribromo-phenol (%)	Biphenyl (%)	Others (%)	Entry
Δ	2	5 eq. TEA	17.5 h	43	52	5	0	1
Δ	3	5 eq. TEA	17.5 h	39	33	20	8	2
Δ	2	1.5 eq. Na ₂ CO ₃	17.5 h	59	8	33	0	3
Δ	3	1.5 eq. Na ₂ CO ₃	17.5 h	39	34	19	8	4
MW	2	1.5 eq. Na ₂ CO ₃	30 min	82	10	8	0	5
MW	3	1.5 eq. Na ₂ CO ₃	30 min	87	11	2	0	6

under microwave conditions, were completed after 30 min and the relative proportion of (4-bromophenyl)benzene (**5**) (obtained after treatment with bromine) was 82 and 87%, respectively. In total, the by-products were formed in 13–18% (Table 1/entries 5 and 6). On MW irradiation, presence of the imidazolium chloride moiety in the reactant (as in **3**) somewhat increased the proportion of the desired product **5** as compared to the case with non-ionic support (**2**). In case of traditional heating, the proportion of **5** obtained with non-ionic support (**2**) was superior as compared to that measured with the ionic ones (**3**) (Table 1/entries 1 and 3 vs. 2 and 4). In the MW-mediated cases, the (4-bromophenyl)benzene **5** was obtained in ca. 50% preparative yields and in a purity of 98%. Intermediates **2** and **4** were identified by FAB-MS, while **3** and **6** were described earlier [9].

In conclusion, both the ionic liquid supported bromobenzene and its neutral analogues were found to be suitable starting materials in the MW-promoted Suzuki–Miyaura coupling with phenylboronic acid, as the reaction was fast and the yields were competent. However, the imidazolium moiety did not offer a considerable extra advantage as compared to the imidazole substituted.

Evidences on the advantage of the application of microwave irradiation in case of ionic liquid supports are to be studied further. This will be the subject of a separate communication in due course.

EXPERIMENTAL

GC-MS was carried out on a Finnigan Automass II. GCQ quadrupole mass spectrometer combined with a capillary gas chromatograph. A 30 m × 0.25 mm 2B-5MS FSQC column with a film layer of 0.25 μm was applied.

Starting materials **1** and **3** were prepared as described earlier [9–11].

Starting material **2** was synthesized by the alkylation of imidazole with equimolar chloromethyl-dimethyl-(4-bromophenyl)silane in the presence of triethylamine under MW irradiation at 120 °C for 2h. Flash column chromatography (3% methanol in chloroform, silica gel) gave the in-

termediate **2** in quantitative yield. FAB-MS: 295 (M+H)⁺ for the ⁷⁹Br and ²⁸Si isotopes.

General Procedure for the Suzuki–Miyaura Couplings and Desilylations

To 0.34 mmol of **2** or **3** (0.10 and 0.11g, respectively) in 4.5 mL of DMF and 0.5 mL of water was added 0.083g (0.68 mmol) of phenylboronic acid, 0.054g (0.51 mmol) of Na₂CO₃ (or 0.23 mL (1.66 mmol) of triethylamine) and 0.012 g (0.01 mmol) of Pd(PPh₃)₄ and the mixture was stirred at 80 °C for an appropriate time under nitrogen. The mixture was then filtered and the volatile components were evaporated. The primary Suzuki product (**4**) from the reaction of **2** was purified by flash column chromatography using silica gel and 3% MeOH in CHCl₃. The Suzuki product (**6**) from the reaction of **3** was used without further purification. To **4** or **6** in 5 mL CHCl₃ was added 0.04 mL (0.78 mmol) of Br₂ at 0 °C. The mixture was stirred for 2 h at 0 °C and then the volatile components were evaporated. The residue obtained was purified by column chromatography (silica gel, with 3% MeOH in CHCl₃) to afford product **5**.

The MW-assisted syntheses were carried out in the same way, but in a Discover CEM reactor at 80 °C (10–20 W) for the given time. The work-up procedure was carried out as above.

Experimental details are listed in Table 1.

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