Poly(ethylene glycol) Supported Liquid Phase Synthesis of Biaryls

Carsten G. Blettner[a,b], Wilfried A. König[a], Wolfgang Stenzel[b], Theo Schotten[b] *

[a] Institute of Organic Chemistry, University of Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany

[b] Beiersdorf - Lilly GmbH, Wiesingerweg 25, D-20253 Hamburg, Germany

Received 16 December 1997

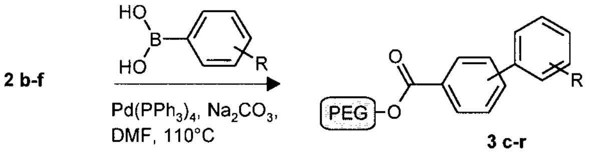
Abstract: The liquid phase synthesis of biaryls via *Suzuki* cross-coupling reaction on poly(ethylene glycol) supports (PEGs) is described. The reaction is exemplified by parallel coupling of polymer bound aryl halides with boronic acids. Four different PEGs were employed as soluble polymer supports for parallel synthesis. The generated libraries include both sterically hindered aryl halides (**2b, 2d**) and boronic acids. The reactions were run in the homogeneous phase and the synthetic sequences performed in parallel fashion. Quantitative conversion in the *Suzuki* couplings was verified by ^{1}H-NMR analysis (**3a-r**). The polymer bound products were isolated in good to excellent (52% to 98%) yields by either simple precipitation of the soluble support or column filtration.

The availability of general reaction protocols for organic molecule libraries which lead to high yields of pure products is essential for the success of combinatorial chemistry. Solid-phase synthesis can be complicated by heterogeneous reaction conditions, the requirement for large quantities of solid support and the difficulty in monitoring reactions.[1] The use of soluble supports offers a method to overcome these difficulties while maintaining the ease of solid phase synthesis.[2] PEG is soluble in most common solvents[3] and has a strong propensity to crystallize.[4] Inclusions due to gelatinous precipitation are avoided.[5] The recent interest in PEG-supported synthesis[6] including liquid phase combinatorial strategies[7] prompted us to report our results.

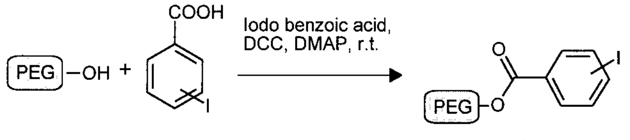
The biaryl subunit is an important pharmacophore in a variety of biologically active compounds.[8] We synthesized small libraries of biaryls via the *Suzuki* cross-coupling reaction[9] of aryl bromides or iodides on four different PEGs. The aryl halides were activated for the cross-coupling reaction by the electron withdrawing effect of the ester linkage to the polymer.[9] Commercially available monofunctional PEG 2000 monomethylether (MeO-PEG 2000), MeO-PEG 5000, difunctional PEG 4000 and PEG 6000 were chosen as polymer supports. Our target was to generate the libraries by using parallel synthesis and to find the most suitable polymer in terms of loading capacity and ease of workup.

5-Bromothiophene-2-carboxylic acid was esterified with MeO-PEG 2000 employing a variation of the DCC/DMAP method.[10] The recovered yield of the product **2a** was 73%. The conversion estimated by NMR was >95%. No starting material was found by MALDI-TOF MS. The iodo benzoic acids were esterified with the soluble polymers employing the same reaction conditions as above (Table 1).[10]

The cross-coupling reaction[9] was readily accomplished on the PEG esters **2a-f**[11] utilizing a variation of standard *Suzuki* conditions. Aqueous DMF was used as a solvent in combination with the weak base Na_2CO_3. The aryl halides were converted quantitatively on the polymer at 110°C overnight. Compared to non-polymer supported liquid phase chemistry higher temperatures were necessary to assure quantitative conversion of **2 a-f** into the *Suzuki* reaction products. Both sterically hindered polymer bound aryl iodides (**2b, 2d**) and sterically hindered boronic acids were chosen as reaction substrates for the reaction (Table 2).



3 c-r



2 b-f

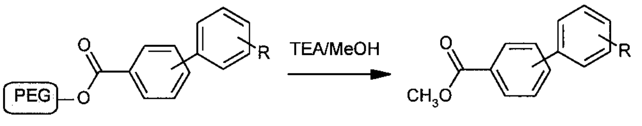
Table 1. Synthesis of Iodo benzoic acid PEG esters

Entry	Polymer	I	2[a]	Recovered Yield [%]	Conversion Yield [%][b]
1	MeO-PEG 5000-OH	o-I	**2b**	93	>95
2	HO-PEG 4000-OH	p-I	**2c**	96	>95
3	HO-PEG 6000-OH	o-I	**2d**	99	>95
4	HO-PEG 6000-OH	m-I	**2e**	97	>95
5	HO-PEG 6000-OH	p-I	**2f**	89	>95

[a] All compounds showed spectroscopic behavior as expected.

[b] Estimated by ^{1}H-NMR. No starting material was detected by MALDI-TOF MS

PEG itself, the ester group and all functional groups remained stable during the reaction process. The desired methyl esters **4a-r** were obtained in parallel fashion by transesterification with triethylamine (TEA) in methanol.[12] This mild cleavage procedure resulted in very pure reaction products but gave variable yields (Table 2).

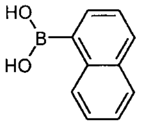
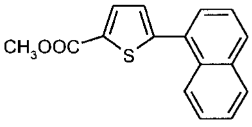
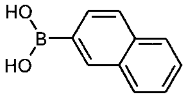
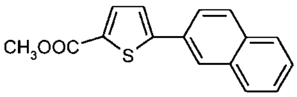
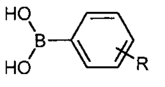
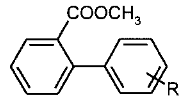
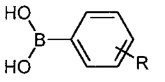
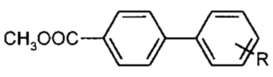
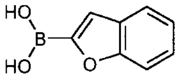
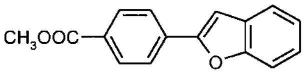
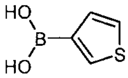
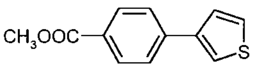
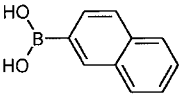
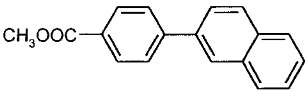
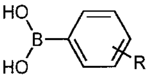
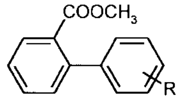
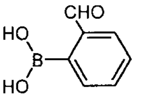
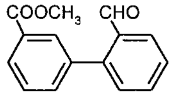
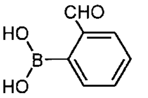
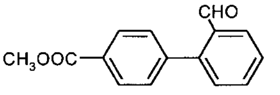


3 c-r **4 c-r**

The polymer bound products **3a-r** were purified either by precipitation of the polymer support into ice cold *tert*-butyl methyl ether[11] (**3a-g, 3o-r**) or by column filtration (**3h-n**).

To ensure crystalline precipitation and high recovery of the polymer bound products in parallel fashion, the right choice of polymer was essential. MeO-PEG 5000 provided crystalline precipitation products under the conditions employed. The recovered yield of the polymer bound biaryls was good to excellent (86-96%, **3c-g**), but the polymer suffered a loading capacity of only 0.2 mmol/g. MeO-PEG 2000 esters **3a** and **3b** provided a loading capacity of 0.47 mmol/g and a recovery of 88 and 97% respectively. The precipitation was strongly influenced by impurities and the ester residue. Crystalline precipitates were only obtained at carefully controlled temperatures below 0°C, thus making the workup less suitable for parallel synthesis of larger libraries. Disubstituted PEG 6000 offered the optimum conditions in terms of loading capacity and workup via the precipitation method. The loading capacity was 0.33 mmol/g and the precipitation property very similar to MeO-PEG 5000. The PEG 6000 bound products **3o-r** were isolated in excellent yields (90-98%) and high purity (Table 3).

Table 2. Suzuki Reaction on PEGs and Subsequent Cleavage with TEA/MeOH

Entry	2	Boronic Acid	3	Recovered Yield [%][a]	Conversion Yield [%][b]	Cleaved Products (Methylester)	4	Yield [%][c]
1	**2a**		**3a**	97	>95		**4a**	90
2	**2a**		**3b**	88	>95		**4b**	83
3	**2b**		**3c**	86	>95		**4c**	93 (R=o-CHO)
4	**2b**		**3d**	96	>95		**4d**	80 (R=m-CHO)
5	**2b**		**3e**	88	>95		**4e**	68 (R=p-CHO)
6	**2b**		**3f**	94	>95		**4f**	46 (R=o-OCH$_3$)
7	**2b**		**3g**	86	>95		**4g**	71 (R=o-Cl, p-Cl)
8	**2c**		**3h**	58			**4h**	69 (R=m-NHCOOCH$_3$)
9	**2c**		**3i**	52	>95		**4i**	91 (R=p-Cl)
10	**2c**		**3j**	71			**4j**	86 (R=o-CHO)
11	**2c**		**3k**	74			**4k**	46 (R=H)
12	**2c**		**3l**	74	>95		**4l**	70
13	**2c**		**3m**	67	>95		**4m**	76
14	**2c**		**3n**	58	>95		**4n**	57
15	**2d**		**3o**	97	>95		**4o**	65 (R=o-CHO)
16	**2d**		**3p**	98	>95		**4p**	87 (R=m-CHO)
17	**2e**		**3q**	90	>95		**4q**	92
18	**2f**		**3r**	96	>95		**4r**	91

[a] Recovered yield of the PEG polymer bound product. **3 h-n** (Polymer **2c**, PEG 4000) were purified by parallel column filtration on silica gel.

[b] Conversion of the PEG bound halide estimated by ^{1}H-NMR (**3a-r**). No starting material could be detected by MALDI-TOF MS (**3a,b,h-n**).

[c] Yield of the transesterification reaction. Confirmed by ^{1}H-NMR and EI-MS data, new compounds gave satisfactory elementary analysis.

Table 3. Loading capacity and purification of applied PEG polymers

Polymer	loading capacity [mmol/g]	compounds	purification method	Recovered Yield [%]
MeO-PEG 5000-OH	0.20	**3c-g**	crystallization	86-96
MeO-PEG 2000-OH	0.47	**3a-b**	crystallization	88, 97
HO-PEG 6000-OH	0.33	**3o-r**	crystallization	90-98
HO-PEG 4000-OH	0.50	**3h-n**	column filtration	52-74

Alternatively to the crystallization method, the *Suzuki* reaction mixtures on PEG 4000 were purified by parallel flash column filtration.[13] The polymer was purified on a short silica gel column by successive elution with *tert*-butyl methyl ether, i-propanol, toluene and ethyl acetate and was finally eluted with warm ethanol. Due to the polydispersity of PEGs distinct tailing was observed and the recovery of polymer **3h-n** was only modest. Although no fragmentation of the polymer was observed under the employed conditions, PEGs are liable to degrade on silica gel.[14]

For parallel synthesis of biaryls on PEGs the precipitation method resulted in good to excellent recovery and high purity of the polymer bound products and was therefore the method of choice. Disubstituted PEG 6000 offered the optimum conditions in terms of loading capacity and ease of workup.

References and Notes

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10. Zalipsky, S.; Gilon, C.; Zilkha, A. *J. Macromol. Sci. Chem. A21*, **1984**, 839. The procedure for esterification of PEG: DCC (4 eq) was taken up in CH_2Cl_2 (2.5 mol/l) and added to a solution of PEG (1 eq OH), iodo benzoic acid or 5-bromothiophene-2-carboxylic acid (4 eq) and DMAP (0.25 eq) in CH_2Cl_2 or CH_2Cl_2/THF mixtures. The reaction mixture was stirred overnight at room temperature. Dicyclohexylurea was filtered off, the volume of the filtrate reduced under vacuum and poured into a tenfold volume of cold *tert*-butyl methyl ether. The crystalline polymer was filtered off and washed with ice cold ethanol. The polymer was dissolved in CH_2Cl_2 and precipitated as above. This procedure was repeated once. TLC (CH_2Cl_2:EtOH, 98:2) only showed the polymer spot. The product was dried overnight under vacuum. The high purity of the compounds (>95%) was estimated by ^{1}H-NMR. The MALDI-TOF MS technique was used to follow the conversion of the starting material quantitatively.
11. The synthesis of PEG bound biphenyl **3g** (entry 7, Table 2) is representative for the parallel *Suzuki* reaction on the PEG-polymer and the purification procedure via the precipitation method: **2b** (1 g, approx. 0.19 mmol) was dissolved in 5 ml distilled DMF and 73 mg (0.38 mmol, 2 eq) 2,4-dichlorophenylboronic acid, 11.6 mg (0.01 mmol, 0.05 eq) tetrakis-(triphenylphosphine)palladium(0) and 0.25 ml (0.5 mmol, 2.5 eq) 2M sodium carbonate were added. The mixture was stirred under argon at 110°C for 10 h in a screw-cap culture tube. Toluene was added and insoluble material removed by centrifugation. The volume of the solution was reduced under vacuum and poured into ice cold *tert*-butyl methyl ether for precipitation. The solution was filtered and washed with ice cold ethanol. The polymer was taken up in CH_2Cl_2 and the procedure repeated twice. TLC (CH_2Cl_2:EtOH, 98:2) did only show the polymer signal. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.06 (1H, d, J = 7.6 Hz); 7.59 (1H, t, J = 7.4 Hz); 7.49 (1H, t, J = 7.5 Hz); 7.44 (1H, s); 7.30 (1H, d, J = 8.2 Hz); 7.23 (1H, d, J = 7.8 Hz); 7.19 (1H, d, 8.2 Hz); 4.24 (2H, t, J = 4.8 Hz); 3.49-3.79 (m, PEG); 3.38 (3H, s).
12. The transesterification of **3g** (entry 7, Table 2) in TEA/methanol is representative for the cleavage procedure: 1g (approx. 0.19 mmol) dry polymer bound biaryl was dissolved in 10 ml dry 20% TEA/MeOH and stirred in a screw-cap culture tube under argon at 85°C for 2d. The mixture was dried under vacuum, taken up in 4 ml CH_2Cl_2, precipitated into ice cold *tert*-butyl methyl ether and filtered. The polymer was washed with ice cold *tert*-butyl methyl ether or EtOH, dissolved in CH_2Cl_2 and precipitated again as above.[11] The volume of the combined filtrates was reduced under vacuum and the crude product purified via column filtration (AcOEt : iso-Hexane; 4 : 1, Rf: 0.68) to give **4g** as a colourless oil. EIMS (70 eV), m/z 245, 230, 186, 152; ^{1}H-NMR (500 MHz, $CDCl_3$): 8.06 (1H, d, J = 7.6 Hz); 7.59 (1H, t, J = 7.4 Hz); 7.49 (1H, t, J = 7.5 Hz); 7.44 (1H, s); 7.30 (1H, d, J = 8.2 Hz); 7.23 (1H, d, J = 7.8 Hz); 7.19 (1H, d, 8.2 Hz); 3.70 (3H, s); Anal. Calcd. for $C_{14}H_{10}Cl_2O_2$: C, 59.81; H, 3.59; Cl, 25.22. Found: C, 60.00; H, 3.53; Cl, 25.24.
13. Column filtration was performed on 63-200 μ silica gel in disposable columns. 5g silica gel was used for one gram PEG 4000.
14. Bayer, E., personal communication.