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Rapid Microwave-Assisted Suzuki Coupling on Solid-Phase

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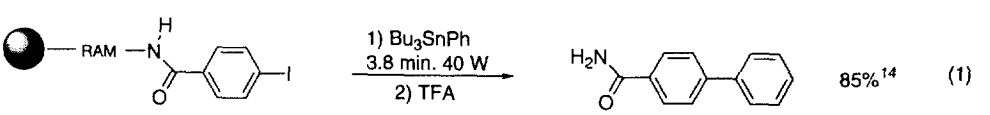
Abstract: Microwave-assisted palladium-catalysed coupling of aryl and heteroaryl boronic acids with iodo- and bromo-substituted benzoic acids, anchored to TentaGel S RAM, provided high isolated yields of coupled products after a reaction time of 3.8 minutes (45 W). Copyright © 1996 Elsevier Science Ltd

The advantages of solid-phase organic chemistry to combinatorial organic synthesis are well recognised.[1] Palladium-catalysed coupling reactions constitute one group of robust reactions with high generality, suitable for combinatorial chemistry. Several examples of successful applications of these reaction types on solid phase have been reported recently,[1a] including the use of the Suzuki coupling.[2-6]

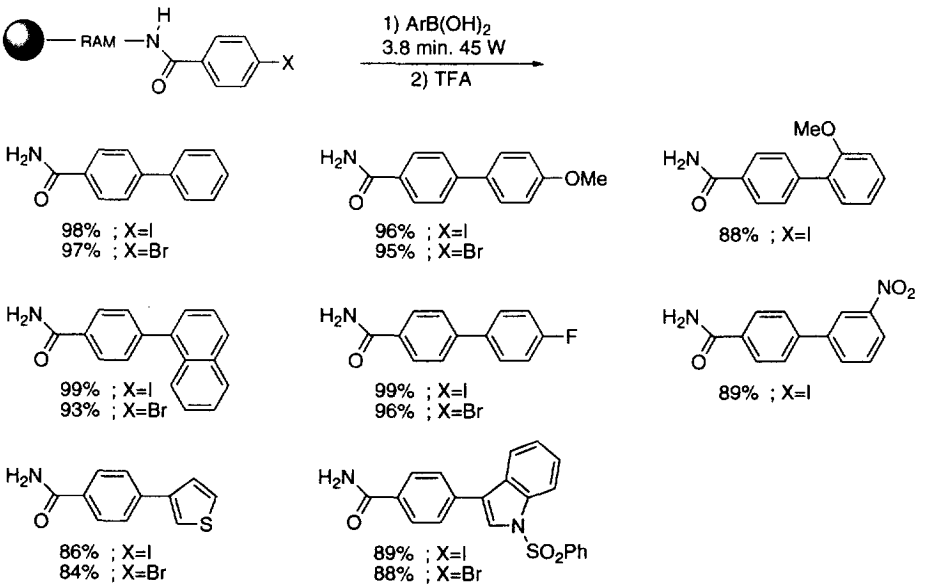
In combinatorial chemistry the reaction times and reaction temperatures required are frequently crucial factors. Microwave irradiation is used to enhance reaction rates.[7] To our knowledge, application of this heating technique to coupling reactions involving labile organopalladium intermediates has not yet been demonstrated. We herein report that microwave assisted Suzuki coupling reactions[8] on PEG (polyethylene glycol) grafted polystyrene[9] bound substrates deliver high yields of products after very short reaction times.

The preparative results are summarised in the Table. We selected eight representative organoboronic acids and reacted these with 4-iodo and with 4-bromobenzoic acid, linked to Rink amide (RAM) TentaGel.[10] An irradiation effect[11] of 45 W was suitable to provide both a >99% conversion of the starting material within 3.8 minutes and a minimal decomposition of the solid support. The coupled product was cleaved from the polymer to afford the free biaryl in excellent yield, accompanied with only a small amount of PEG.[12] In addition, we performed a microwave assisted Stille reaction[13] on the polymer tethered 4-iodobenzoic acid (Equation 1).



85%[14] (1)

Table. Suzuki Coupling on Solid-Phase Assisted by Microwave Irradiation.[15,16]



In summary, we have demonstrated that the Suzuki coupling assisted by microwave irradiation provides an efficient procedure for rapid C-C bond formation.

General procedure for the Suzuki coupling reactions: A sealed pyrex tube[17] was charged, under nitrogen, with 4-iodo or 4-bromo functionalised resin (100 mg, loading ~0.23 mmol/g), $Pd(PPh_3)_4$ (1.15 mg, 0.0010 mmol), aryl boronic acid (0.20 mmol), 2M Na_2CO_3 (0.10 ml, 0.20 mmol), H_2O (0.30 ml), EtOH (0.19 ml) and DME (0.75 ml).[18] After irradiation, the mixture was cooled to room temperature. The resin was thereafter transferred to a 3-ml disposable syringe equipped with a porous polyethylene filter using H_2O/DME, washed with successive portions of H_2O, DME, DMF, sat. KCN/DMSO,[19] MeOH, H_2O, MeOH and DCM (2 x 3 ml each) and dried. The resin was treated with 99% aq. TFA for 1 h, filtered and washed with 0.5 ml TFA and 2 x 0.5 ml DCM. The filtrates were combined and evaporated to dryness to yield the biaryl.

Procedure for the Stille coupling reaction: 4-Iodo functionalised resin (100 mg, loading ~0.23 mmol/g), Pd_2dba_3 (1.05 mg, 0.00115 mmol), $AsPh_3$ (2.11 mg, 0.0069 mmol), phenyltributyltin (73.4 mg, 0.20 mmol) and dry NMP (1.0 ml) were placed in a pyrex tube[17] under nitrogen. The tube was closed, positioned in the cavity and irradiated for 3.8 min. at 40 W. After cooling, the product was washed and cleaved from the resin as described for the Suzuki reactions. (85% Isolated yield,[15,16] >99% conversion.)

Acknowledgement. We gratefully acknowledge the support from the Swedish Natural Science Research Council.

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9. 90 μm Fmoc TentaGel S RAM-resin (S30 023, 0.23 mmol/g capacity) purchased from Rapp Polymere.
10. The 4-halobenzoic acids (4 eq.) were coupled to deprotected resin using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate (HBTU, 4 eq.) and DIEA (8 eq.) for 2 h. Remaining amino groups were then capped by acetylation
11. Microwave heating was carried out with a MicroWell 10 single-mode microwave cavity producing constant irradiation (2450 MHz), Labwell AB, Östra Ågatan 51 A, S-753 22 Uppsala, Sweden. e-mail: Soren Nygren@Labwell.se **CAUTION! Suitable precautions should always be taken with reactions carried out in closed vessels due to the risk of explosion.**
12. Release of PEG was observed also from the non-functionalised resin. 150 mg Fmoc TentaGel S RAM-resin was deprotected with 20% piperidine/DMF and was treated thereafter with 99% aq. TFA for 1h (cleavage conditions). This procedure afforded 2.8 mg crude PEG.
13. The use of $AsPh_3$ as ligand in Stille reactions is recommended by Farina. a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, 113, 9585. Stille reactions on support-bound aryl halides have recently been reported: b) Deshpande, M. S. *Tetrahedron Lett.* **1994**, 35, 5613, c) Forman, F. W.; Sucholeiki, I. *J. Org. Chem.* **1995**, 60, 523.
14. No butyl transfer product was detected by GC/MS or ^{1}H-NMR.
15. Isolated yield (based upon the capacity of the Fmoc TentaGel S RAM-resin). Determined after correction (by ^{1}H-NMR) for the released PEG in the cleavage step.

16. All products gave satisfactory ^{1}H-NMR spectra (DMSO-D6) as well as appropriate ion identification by mass spectrometry (EI or PDMS) and had purity >95% by GC/MS.
17. The reactions were performed in heavy-walled pyrex tubes (8 ml, l=150 mm) equipped with screw caps and silicon septa. The reaction volume filled not more than 1 / 5th of the total volume of the tube, thereby allowing head space for pressure build-up during the microwave treatment.
18. DME was introduced as solvent in the Suzuki reaction by Gronowitz. Gronowitz, S.; Bobosik, V.; Lawitz, K. *Chem. Scr.* **1984**, 23, 120.
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