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Solid Supported Aryl/heteroaryl C–N Cross-coupling Reactions.

Andrew P. Combs*, Simon Saubern[1], Maria Rafalski and Patrick Y.S. Lam

DuPont Pharmaceuticals Company, Chemical and Physical Sciences Department, Experimental Station, P.O. Box 80500, Wilmington, DE 19880-0500, USA.

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Abstract: We report herein the first examples of polymer supported aryl-heteroaryl C–N cross-coupling reactions and dramatically decreased reaction times upon microwave irradiation. The methodology provides easy access to *N*-arylated heterocycles from heterocycles bearing an N–H bond and readily available arylboronic acids in the presence of copper(II) acetate and pyridine.
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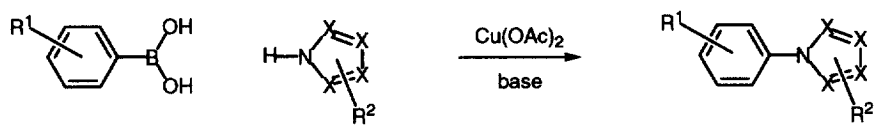
Keywords: Arylation; Coupling reactions; Microwave heating; Polymer support.

N–Arylated heterocycles comprise an important class of compounds often associated with biological activity.[2] Our recently reported[3] copper(II) mediated *N*–arylation of heterocycles represents an important new and simple methodology for preparing compounds containing this functionality (Scheme 1). We wished to take advantage of this synthetic transformation on a solid support to prepare diverse libraries of *N*–arylated heterocycles for broad biological screening. A general method for the solid phase synthesis of *N*–arylated benzimidazoles, imidazoles, triazoles and pyrazoles is presented herein.

Scheme 1. Copper(II) mediated *N*–arylation of heterocycles.[3]



X = CH or N
R^1, R^2 = subsituents or benzofused

The feasibility of performing the copper(II) mediated *N*–arylation reaction on a solid support was initially investigated for the benzimidazole nucleus. This heterocycle was chosen since the solution phase reaction between benzimidazole and *p*-tolylboronic acid proceeds in good yields (67%) at room temperature[3] and therefore would be more likely to translate to solid phase. Benzimidazole-5-carboxylic acid was coupled to polystyrene–polyethyleneglycol (PS–PEG) resin[4] employing the PAL-linker using EDC·HCl as the coupling reagent to afford benzimidazole derivative (**1**).

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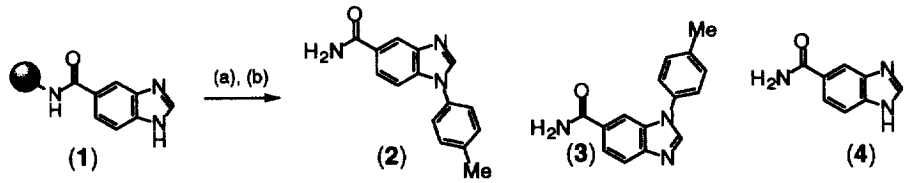
Scheme 2. Copper(II) mediated *N*–arylation of the benzimidazole (**1**) with *p*-tolylboronic acid.



(a) $Cu(OAc)_2$ (5 eq), 4-$MePhB(OH)_2$ (3 eq), pyridine–NMP (1:1); (b) TFA–CH_2Cl_2 (1:1)

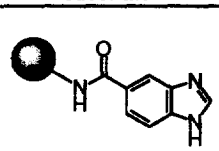
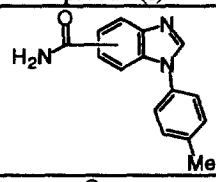
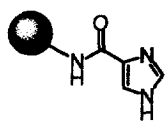
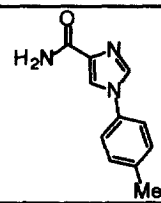
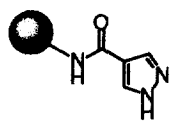
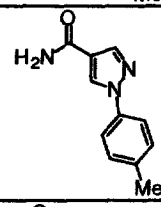
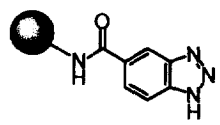
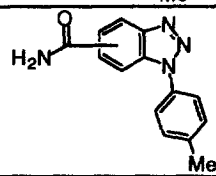
Initial attempts to *N*–arylate solid supported benzimidazole (**1**) at ambient temperature for 48 h provided low yields of *N*–arylated derivatives (**2**) and (**3**). The predominant product isolated was the unsubstituted benzimidazole (**4**) (Scheme 2). Considerable experimentation demonstrated that a 1:1 mixture of pyridine and *N*–methylpyrrolidinone (NMP) was the most versatile base and solvent combination for the resin bound version of this reaction, dissolving a variety of boronic acids while providing good yields of the desired products. We also noted that molecular sieves and air (presumably oxygen) were necessary to improve yields.[5] These results are similar to those reported by Evans[6] with copper(II) mediated *O*–arylation reactions.

Reaction of solid supported benzimidazole (**1**) under the optimized conditions of 5 equivalents of 4-$MePhB(OH)_2$ and 3 equivalents of $Cu(OAc)_2$ in pyridine–NMP (1:1) at 80° for 48 h gave approximately 30% yield by ^{1}H-NMR of (**2**) and (**3**) in a 1:1 ratio (the remaining material being (**4**)). Multiple couplings (3–5 times) could be performed to drive the reaction to completion, as HPLC assessed by lack of starting material in the crude cleaved product. The moderate yields (~60% based on initial resin loading) isolated reflect the incomplete loading of the heterocycle to the solid-phase. Even so, we felt that the 48 h cycle time was too lengthy to be of practical use in preparing libraries of *N*–arylated heterocycles.

Microwave irradiation[7] to decrease reaction times and increase yields of solid supported reactions has been successfully demonstrated for solid supported palladium catalyzed couplings[8] and was therefore investigated for these reactions. Irradiation of the polymer supported reaction in a domestic 1000 W microwave oven at full power for 3 x 10 s, with manual agitation between each interval gave yields comparable to heating for 48 h at 80°. The cycle time was effectively reduced from 48 h to less than 5 minutes. After 5 cycles (addition of fresh reagents, microwave 3 x 10 s, wash resin), we were unable to detect any remaining (**4**) after cleavage of the products from the resin and isolated the desired *N*–arylated products (**2**) and (**3**) in 56% yield and 96% purity. It should be noted that arylation of the benzimdazole amide nitrogen was not observed, even though Chan[9] has reported *N*–arylation of amides under similar conditions.[10]

To assess the versatility of this reaction on solid support, various heterocycle-carboxylic acids were coupled to PS-PEG resin via the PAL linker (Table 1). *N*–arylation of these solid supported derivatives under the optimized microwave conditions and cleavage with TFA gave the desired *N*–arylated heterocycles in good yields (56–64%) and excellent purities (73–97%) without further optimizations. Noteworthy is the dramatically increased yield (55%) for the benzotriazole derivative (entry 4) when compared to the solution phase reaction of benzotriazole itself, which only provided 11% yield[11] of the desired product at room temperature. The ability to drive these solid phase reactions to completion with multiple additions of excess reagent and simple purification by washing away the unreacted reagents demonstrates the utility of this method.[12]

Table 1. Coupling of *p*-tolylboronic acid to various polymer bound heterocyles.[a]

entry	substrate[b]	product(s)	yield[c]	purity[d]	ratio of regioisomers[e]
1.			56%	96%	1:1
2.			60%	73%	—
3.			64%	84%	—
4.			55%	97%	1:1

(a) 3 equivalents of 4-MePhB(OH)2, 5 equivalents of Cu(OAc)2, 200mg powdered 4Å molecular sieves per 1g resin, pyridine–NMP (1:1), microwave heating 3 x 10s, 5 applications of reagents.
(b) Entries 1,2 and 4 were prepared from PEG–PS resin (PAL linker), the appropriate heterocylcecarboxylic acid and EDC·HCl. Entry 3 was prepared from PEG–PS resin (PAL linker) and the acid chloride of pyrazole-4-carboxylic acid.
(c) Cleaved products were passed through a small plug of silica gel (50 mg) using CH_2Cl_2 as eluant. Yields were determined based on initial resin loading (0.29mmol/g).
(d) Determined by HPLC at 220 nm, 4 mm x 20 mm RP C-18 5 μm column, linear gradient H_2O/CH_3CN/TFA.
(e) Ratio of regio isomers was determined by ^{1}H-NMR integration of the arylmethyl singlets.

The solid phase synthesis of *N*–arylated heterocycles has been demonstrated utilizing copper(II) mediated couplings of arylboronic acids to polymer bound benzimidazoles, imidazoles, triazoles, and pyrazoles. Microwave irradiation efficiently promotes the coupling process and affords high yields and purities of the desired products. The translation of this methodology to a suitable high density format promises access to large numbers of diverse *N*–arylated heterocycles for biological screening.

Acknowledgments. We thank Dr. Dominic M.T. Chan for early access to his original work in copper(II) mediated arylation reactions and Prof. David Evans for stimulating and helpful discussions during this research.

Experimental:

Caution! As exposure to oxygen is apparently important to ensure high yields in this reaction[3,6] it is not necessary to use sealed reaction vessels. Nevertheless, precautions should be taken to ensure that rapid microwave heating does not cause bumping of the reaction mixture.

Typical Procedure: A stock solution of *p*-tolylboronic acid (500 mg) in pyridine (12.5 mL) and *N*-methylpyrrolidinone (12.5 mL) was dried over 4Å molecular sieves (beads) for 3 h. Copper(II) acetate (45 mg, 0.25 mmol), powdered 4Å molecular sieves (50 mg), resin (**1**) (255 mg, 0.29 mmol/g PS–PEG) and boronic acid stock solution (1 mL, 0.15 mmol) were placed in a loosely capped glass vial, and heated for 3 x 10 s in a domestic 1000 W Sharp carousel microwave oven at full power. Between each heating, the reaction was agitated manually until it had cooled to room temperature. The resin was filtered off and washed with pyridine–THF (1:1) until the washings were colourless. The resin was again treated as above until all of the stock solution had been consumed. The resin was washed with MeOH, CH_2Cl_2 and MeOH and dried *in vacuo*. The product was then cleaved from the resin (100mg) by treatment with a 1:1 mixture of CF_3CO_2H and CH_2Cl_2 for 40 min at room temperature, solvent evaporated to dryness and the resulting oil dissolved in CH_2Cl_2 and passed through a small plug of silica gel (50 mg) using CH_2Cl_2 as eluant to provide a 1:1 mixture of the benzimidazoles (**2**) and (**3**) (4.1 mg, 56%); 1-*N*-(4-Methylphenyl)-5-benzimidazolecarboxamide (**2**) ^{1}H-NMR δ (300MHz, CD_2Cl_2/CF_3CO_2D) 9.30 (1H, s, 2-H), 8.61 (1H, brs, 4-H), 8.25 (1H, brd, J = 8.8 Hz, 6-H), 7.90 (1H, d, J = 8.8 Hz, 7-H), 7.60 (2H, d, J = 8.0 Hz, 2'-H, 6'-H), 7.54 (2H, d, J = 8.0 Hz, 3'-H, 5'-H), 2.57 (3H, s, 4'-Me); *m/z* (+ES) 252 (100%, M+H$^+$);3-*N*-(4-Methylphenyl)-5-benzimidazolecarboxamide (**3**)^{1}H-NMR δ (300MHz, CD_2Cl_2/CF_3CO_2D) 9.29 (1H, s, 2-H), 8.31 (1H, brs, 4-H), 8.24 (1H, brd, J = 8.8 Hz, 6-H), 8.16 (1H, d, J = 8.8 Hz, 7-H), 7.60 (2H, d, J = 8.0 Hz, 2'-H, 6'-H), 7.54 (2H, d, J = 8.0 Hz, 3'-H,5'-H), 2.57 (3H, s, 4'-Me); *m/z* (+ES) 252 (100%, M+H$^+$).

A sample of unreacted resin (**1**) was treated with a 1:1 mixture of CF_3CO_2D and CD_2Cl_2 for 40 min at room temperature to afford 5-benzimidazolecarboxamide (**4**) ^{1}H-NMR δ (300MHz, CD_2Cl_2/CF_3CO_2D) 9.41 (1H, s, 2-H), 8.57 (1H, brs, 4-H), 8.21 (1H, brd, J = 8.8 Hz, 6-H), 8.08 (1H, d, J = 8.8 Hz, 7-H); *m/z* (+ES) 162 (100%, M+H$^+$).

REFERENCES AND NOTES

1. Current address: CSIRO Molecular Science, Private Bag 10, Clayton South MDC, Clayton VIC 3169, Australia.
2. A search of the CMC database of biologically active compounds revealed *N*–arylated heterocycles possessing analgesic, antiinflammatory, antimicrobial, antiasmatic, antibacterial and antirheumatic properties, among others.
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8. Larhed, M; Lindeberg, G.; Hallberg A., *Tetrahedron Lett.*, 1996, **37**, 8219–8222.
9. Chan, D.M.T.; Monaco, K.L.; Wang, R.-P. and Winters, M.P., *Tettrahedron Lett.*, 1998, **39**, 2933–2936.
10. We have been unable to arylate a variety of amides under these conditions.
11. Unpublished results in this laboratory.
12. Suitably adapted 96 well microtiter plates have been utilized for microwave irradiation of reactions in our labs. This technology provides an efficient means of library production, though we have measured with a a thermocouple probe considerable temperature gradients (10-20 degree C) between the outer and inner wells of microtiter plates upon microwave irradiation, leading to non-uniform heating of reactions in this format.