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Copper-catalyzed coupling of (*S*)-1-(3-bromophenyl)-ethylamine and N–H containing heteroarenes using microwave heating

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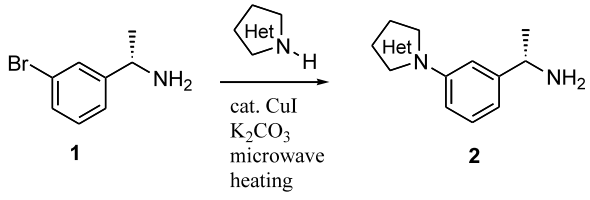
Abstract—The Ullmann coupling of (*S*)-[1-(3-bromophenyl)-ethyl]-ethylamine (**1**) with a variety of N–H heteroarenes using microwave heating is described.

During the course of a medicinal chemistry program, we wanted to convert (*S*)-1-(3-bromophenyl)-ethylamine (**1**) to the *N*-arylimidazole **2a** through a copper-mediated Ullmann coupling reaction[1] with imidazole (Table 1). The Ullmann type *N*-arylation of 6-nitroindazole with 2-bromobenzoic acid was previously reported, and the optimized conditions utilized copper(I) iodide (10 mol%) and potassium carbonate (1.1 equiv.) in DMF at 100°C.[2] Recently, Buchwald et al. demonstrated that the *N*-arylation of imidazoles can be accomplished using $(CuOTf)_2$·benzene as a copper source and Cs_2CO_3 as a base in the presence of 1,10-phenanthroline (phen) and *trans*,*trans*-dibenzylideneacetone (dba) as additives in xylenes at 110–125°C.[3] This methodology has been extended to coupling reactions with other N–H containing heteroarenes using racemic *trans*-1,2-cyclohexanediamine as a ligand and copper(I) iodide as the copper source, thus obviating the need of air-sensitive copper(I) triflate.[4] In our case, very little product was formed when a mixture of bromide **1**, imidazole (2 equiv.), copper(I) iodide (10 mol%) and potassium carbonate (1.1 equiv.) in DMF in a sealed tube was heated at temperatures $\geq$100°C. Treatment of **1** with imidazole (1.5 equiv.), $(CuOTf)_2$·benzene (5 mol%) and Cs_2CO_3 (1.1 equiv.) in the presence of phen (1 equiv.) and dba (5 mol%) in xylenes at 110°C furnished **2a** in 20% yield. Surprisingly, compound **2a** was not formed at all when the coupling reaction was carried out with copper(I) iodide (1 mol%), potassium phosphate (2.1 equiv.) and racemic *trans*-1,2-cyclohexanediamine (10 mol%) in dioxane at 110°C for 22 h. After some experimentation, we found that microwave heating can be used to facilitate the Ullmann type *N*-arylation of imidazoles.

Table 1. Copper-catalyzed *N*-arylation of N–H heteroarenes with **1**



1 **2**

Compd	Het–N–H	Time (h)	Yield[a] (%)
2a	Imidazole	2	76
2b	2-Methyl-imidazole	3	68
2c	Benzoimidazole	2	88
2d	Pyrazole	2	91
2e	4-Methylpyrazole	1	90
2f	3-Methylpyrazole	17	65[b,c]
2g	3,5-Dimethylpyrazole	22	49[b]
2h	Indazole	2	72
2i	1,2,4-Triazole	1	96
2j	Pyrrole	3	66
2k	Indole	3	76

[a] Isolated yields (not optimized, one run only).
[b] 2 additional equiv. of heteroarene was added after 1 h.
[c] 1:1 mixture of regioisomers.

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Microwave irradiation has become increasingly popular in recent years to improve the yield and shorten reaction times in a variety of reactions.[5] However, to our knowledge, the microwave-mediated methodology on the Ullmann type *N*-arylation of N–H containing heteroarenes with aryl halides has not yet been reported.[6,7] This report describes our preliminary studies on (*S*)-1-(3-bromophenyl)-ethylamine (**1**) under microwave conditions.[8]

Treatment of aryl bromide **1** with 2 equiv. imidazole in the presence of copper(I) iodide (10 mol%) and potassium carbonate (2 equiv.) in *N*-methylpyrrolidinone (NMP) at 195°C for 2 h under microwave irradiation provided *N*-arylimidazole **2a** in 75% yield after purification of the crude product using silica gel flash chromatography. As a control experiment, the same reaction mixture was heated at 195°C for 2 h in a sealed tube using an oil bath, and **2a** was obtained in 61% yield. This observation demonstrates the advantage of microwave radiation over conventional heating techniques. In another control experiment, **1** was treated with 2 equiv. imidazole and potassium carbonate (2 equiv.) in NMP at 195°C for 2 h under microwave irradiation, and no product was formed. This result shows the requirement of copper(I) iodide as a catalyst in the formation of **2a**. Of special note is that no epimerization occurred under these basic conditions. As shown in Table 1, these conditions worked well not only for imidazoles but also for pyrazoles, pyrrole, indole and 1,2,4-triazole. The *N*-arylation reactions of both 3-methylpyrazole and 3,5-dimethylpyrazole were sluggish presumably due to steric effects, and these reactions were still incomplete even with long reaction times and an additional 2 equiv. of these heteroarenes. In the case of 3-methylpyrazole, a 1:1 mixture of the regioisomers were obtained. A salient feature of this chemistry is that the free amine functionality is well tolerated. It should be noted that the full cleavage of the *N*-BOC group and partial cleavage of the *N*-CBZ group occurred under these conditions. For example, when the *N*-BOC derivative of **1** was exposed to imidazole under the above conditions, amine **2a** was formed exclusively. The scope of this microwave-mediated *N*-arylation reactions were briefly investigated. Thus, treatment of benzoimidazole with bromo- and iodo-benzene in the presence of copper(I) iodide (10 mol%) and potassium carbonate (2 equiv.) under the above microwave conditions afforded *N*-phenyl-benzoimidazole in 60%, 87% yields, respectively. In the case of chlorobenzene, very little product was formed even after 20 h microwave heating.

In summary, we have developed an operationally simple and efficient method for the *N*-arylation of N–H containing heteroarenes with (*S*)-[1-(3-bromophenyl)-ethyl]-ethylamine (**1**) using microwave heating.[9] This methodology appears to be general to the Ullmann type *N*-arylation reactions with other aryl bromides and iodides.

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8. The microwave unit used in our experiments is the Smith Creator® from Personal Chemistry. It continuously adjusts the applied wattage to maintain the desired temperature. Reactions were conducted in the Personal Chemistry proprietary 5 mL sealed vials.
9. Representative procedure: To a solution of (*S*)-1-(3-bromophenyl)-ethylamine (**1**) (100 mg, 0.5 mmol) and indole (117 mg, 1 mmol) in *N*-methylpyrrolidinone (0.67 mL) in a microwave vial were added potassium carbonate (138 mg, 1 mmol), and copper (I) iodide (9.5 mg, 0.05 mmol). The vial was sealed and heated in a Smith Creator® at 195°C for 3 h. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated in vacuo, and the residue was purified by silica gel flash chromatography (10% MeOH/89% EtOAc/1% triethylamine) to give (*S*)-1-(3-indol-1-yl-phenyl)-ethylamine (**2k**) (90 mg, 76% yield) as an oil. ^{1}H NMR (CD_3OD, 400 MHz) δ 1.42 (d, 3H, $J=6.8$ Hz), 4.12 (1H, q, $J=6.8$ Hz), 4.83 (2H, s), 6.62 (1H, dd, $J=0.4$, 3.20 Hz), 7.08 (1H, t, $J=8.0$ Hz), 7.15 (1H, t, $J=8.0$ Hz), 7.38–7.42 (3H, m), 7.50–7.53 (3H, m), 7.58 (1H, d, $J=7.6$ Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 25.28, 52.17, 104.56, 111.43, 121.32, 122.05, 122.83, 123.36, 123.79, 125.18, 129.04, 130.94, 131.01, 137.27, 141.48, 150.12.