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Synthesis of N-arylated sultams: palladium- and copper-catalyzed cross coupling of aryl halides with 1,4-butane and 1,3-propanesultams

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Abstract—Palladium-catalyzed cross coupling of 1,4-butanesultam and 1,3-propanesultam with a variety of aryl halides was found to provide the desired products in 62–93% isolated yield using Xantphos as ligand. The Pd-catalyzed reaction was found to be superior to the analogous Cu-catalyzed reaction based on product yields, reaction rates, and substrate scope.

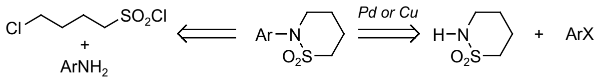
The transition metal-catalyzed coupling of sulfonamides with aryl halides has recently received considerable attention.[1] This is due, in part, to the fact that a large number of biologically active and important compounds contain an aryl sulfonamide, and to the realization that the coupling strategy to form the aryl–N bond provides a new and unique vantage point for diversity-orientated synthesis as well as total synthesis.

N-substituted 1,4-butanesultams and 1,3-propanesultams are a class of cyclic sulfonamides that have been known for years.[2] Compounds containing the sultam moiety have been found to possess pharmacological activity and therefore the synthesis of families of these compounds has been of interest.[3] The most common preparation of N-substituted sultams involves reaction of 4-chloro-butane sulfuryl chloride, which must be prepared, with the appropriate amine followed by dehalogenative ring closure.[4]

Recently, a convenient preparation of both N–H 1,4-butanesultam and 1,3-propanesultam from commercially available starting materials has been disclosed.[5] With these sultams readily available, a transition metal-catalyzed cross coupling protocol would represent a new and rapid method for the preparation of a wide variety of five and six-membered *N*-aryl sultams from readily accessible starting materials (Scheme 1).[6]

The Ullmann coupling is the classic method to perform this reaction.[7] Attempts to apply standard Ullmann coupling conditions (Cu_2O, 2,2′-bipyridine, K_3PO_4, NMP, 120 °C, 12–24 h) with a variety of aryl halides and the 1,4-butanesultam afforded the coupled product in low to moderate assay yields (Table 1). These reactions typically show low rates of conversion to product, even at 120 °C, while exhibiting poor reaction profiles as determined by HPLC. The only substrate exhibiting clean coupling is 2-bromopyridine. Control experiments wherein the copper was omitted resulted in only trace product.[8]

We therefore screened palladium based systems and found that the conditions recently reported by Buchwald for the coupling of amides and sulfonamides with aryl halides utilizing the Xantphos ligand were the most efficient.[9,10] We have found that this protocol works well when applied to both the 1,4-butane and 1,3-propanesultams. Our results for the 1,4-butane sultam are shown in Table 2.



Scheme 1.

Keywords: Sultam; Palladium.

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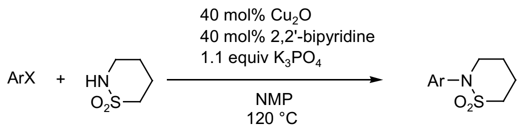
Table 1. Copper catalyzed N-arylation of 1,4-butanesultam



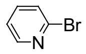
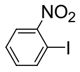
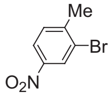
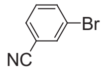
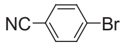
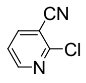
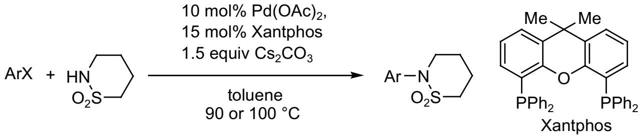
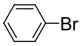
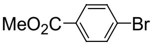
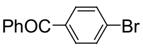
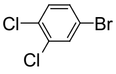
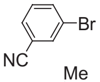
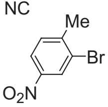
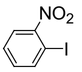
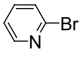
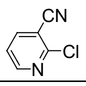
Entry	ArX	Temperature (°C)	Time (h)	Assay yield (%)
1		120	6	93
2		120	18	44
3		120	48	50
4		120	24	35
5		120	15	63
6		120	36	35

Table 2. Palladium-catalyzed N-arylation of 1,4-butanesultam



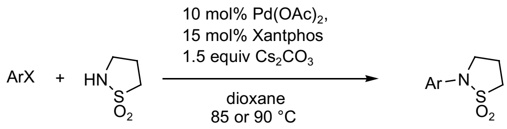
Entry	ArX	Temperature (°C)	Time (h)	Isolated yield (%)
1		100	28	80
2		100	3	89
3		100	4	83
4		100	19	79
5		90	4	82
6		90	5	70
7		90	3	70
8		100	6	62
9		100	17	80

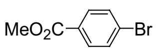
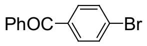
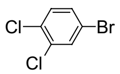
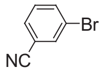
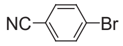
A survey of various aryl bromides revealed that the rate of reaction was significantly faster with aryl bromides possessing strongly electron withdrawing groups such as an ester (entries 2 and 3), nitrile (entry 5), or nitro group (entry 6). Reactions using these substrates provided the coupled product in 3–4 h in toluene at 90 or 100 °C. On the other hand, 4-bromo-1,2-dichlorobenzene requires 19 h to reach completion illustrating the weaker electron withdrawing capabilities of a chlorine substituent. This coupling method is tolerant of *ortho* substitution as illustrated in entry 6. Clearly, electronic activation of the aryl bromide is important since 2-bromotoluene shows little conversion after 24 h at 100 °C. Similarly, 4-bromotoluene shows minimal conversion. Bromobenzene is a viable substrate (entry 1) but the 28 h reaction time is the longest of any aryl halide. In general, aryl halides with electron donating groups are not good substrates for this coupling reaction.[11]

Phenyl triflate does afford a small amount of coupled product, but several byproducts are also observed by HPLC. An aryl iodide, 1-iodo-2-nitrobenzene, is a viable substrate (entry 7), and this example again illustrates that *ortho* substitution is tolerated as long as the substrate is electronically activated. This particular reaction is a palladium catalyzed process since a control experiment where $Pd(OAc)_2$ was not added to the reaction afforded ~1% conversion after 3 h at 100 °C.[12]

2-Bromopyridine reacts rapidly to afford the coupled product (entry 8) while 3-bromopyridine showed little conversion. The greater reactivity of 2-bromopyridine could be due to either the activating effect of a heteroatom alpha to a carbon–halogen bond or coordination of the nitrogen atom to the metal. Aryl chlorides are good substrates when activated by both an electron withdrawing group and a heteroatom. Thus, 2-chloro-3-cyanopyridine afforded product after 17 h (entry 9), while 2-chloropyridine afforded no product after 17 h at 100 °C.

Table 3. N-arylation of 1,3-propanesultam



Entry	ArX	Temperature (°C)	Time (h)	Isolated yield (%)
1		90	6	74
2		85	18	93
3		85	18	88
4		85	24	74
5		85	10	88

1,3-Propanesultams are also effective as coupling partners (Table 3). With this substrate class, dioxane was found to be a superior solvent than toluene and the reactions are in general slower than with the 1,4-butanesultam. The only difference in substrate scope between the two classes of sultams is that bromobenzene was not an efficient coupling partner with the 1,3-propanesultam.

In conclusion, a palladium based catalyst system affords a wide range of N-arylated five and six membered ring sultams directly from an easily accessible sultam and an aryl halide under mild conditions.[13] To the best of our knowledge, this is the first use of a sultam in a cross-coupling reaction and this approach offers a straightforward preparation of a family of N-arylated sultams.

Acknowledgements

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References and notes

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10. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048.
11. In the case of 2-(3-bromophenyl)-1,3-dioxalane the coupling reaction with 1,4-butane sultam was not clean. Attempted coupling of 2-bromo anisole with 1,4-butane sultam resulted in low conversion. In a single experiment we isolated ~30–40% of the coupling product of 1,4-butane sultam with 3-bromoanisole.
12. Under similar conditions, 1,4-butane sultam and phenyl iodide afforded arylated product but the reaction suffers from slow conversion and formation of unidentified products.
13. General procedure: A Schlenk flask was charged with 1,4-butane-sultam (817 mg, 6.05 mmol), palladium acetate (104 mg, 0.465 mmol), Xantphos (405 mg, 0.698 mmol) and cesium carbonate (2.27 g, 6.98 mmol). Toluene (4 mL) was added, followed by methyl 2-bromobenzoate (1 g, 4.65 mmol). The flask was then capped with a septum. The flask was evacuated and refilled with nitrogen, this procedure was repeated a total of three times. The flask was placed into a 100 °C oil bath for 3 h and then cooled to room temperature and diluted with dichloromethane (20 mL). The slurry was filtered through a pad of solka-floc and the pad washed with additional dichloromethane (20 mL). The volatiles were removed and the crude material was chromatographed on silica gel (50:1 to 25:1 CH_2Cl_2/EtOAc) to afford the product as a white solid (1.12 g, 89%).