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Zinc-mediated intramolecular acyl and imino transfer reactions of aryl iodides

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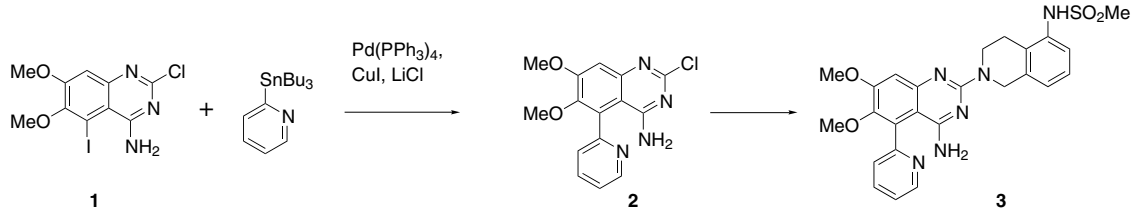
Abstract—A method for the coupling of acyl and imino substituents to the sterically encumbered 5-position of a 4-aminoquinazoline was developed. Starting with a 4-amino-5-iodoquinazoline, the method employs a facile intramolecular zinc-mediated transfer from the 4-amino group to the iodo-bearing carbon. The method was found to be effective for a variety of substituents, in particular a pyridyl group required for the synthesis of Pfizer's prostate selective α_1 antagonist candidate for the treatment of benign prostatic hyperplasia, UK-338,003.

Formation of carbon–carbon bonds in sterically crowded positions of functionalized molecules is a difficult challenge in synthetic organic chemistry. The coupling of a 2-pyridyl substituent to the congested 5-position of the 4-aminoquinazoline **1** was a key step in a synthesis of Pfizer's prostate selective α_1 antagonist candidate for the treatment of benign prostatic hyperplasia, UK-338,003 **3** (Scheme 1).[1–3] The existing method for this coupling employed a 2-pyridyltin reagent. However, the toxicity of organotin compounds makes the use of this reagent unattractive in the synthesis of a pharmaceutical substance. Organozinc compounds are very useful and versatile reagents in organic synthesis, being reactive in C–C bond-forming processes such as Pd- and Ni-catalyzed cross-coupling (Negishi coupling), yet compatible with a wide range of functionality.[4–6] Owing to their lower toxicity and other advantageous properties described above, we were attracted to the use of organozinc reagents in this step.

Initially, we used 2-pyridylzinc chloride[7] in this reaction in place of 2-tributylstannylpyridine (Scheme 2). 2-Pyridylzinc chloride was prepared from 2-bromopyridine by halogen–metal exchange with isopropylmagnesium chloride,[8–10] followed by addition of zinc chloride. The desired coupling reaction took place, but was accompanied by substantial reduction to **4**. We were unable to achieve more than a 1:1 ratio of **2**–**4** in this reaction.



Scheme 1. Synthesis of UK-338,003 employing 2-(tributylstannyl)pyridine.

Keywords: Organozinc reagent; Cross-coupling reactions; Negishi coupling; Heterocyclic chemistry; Aromatic substitution.
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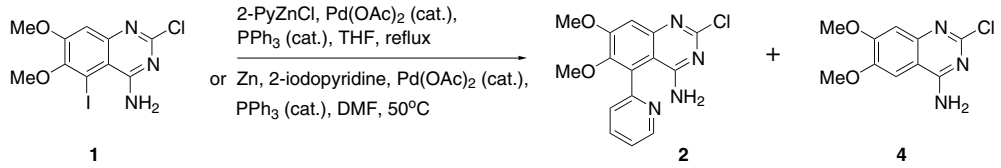
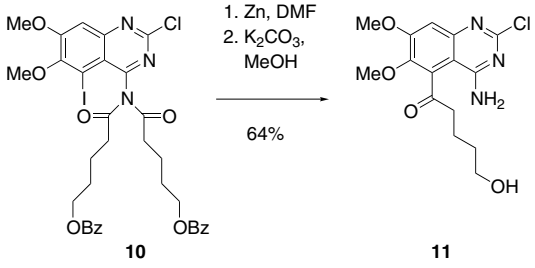


Scheme 2. Negishi couplings of iodide **1**.

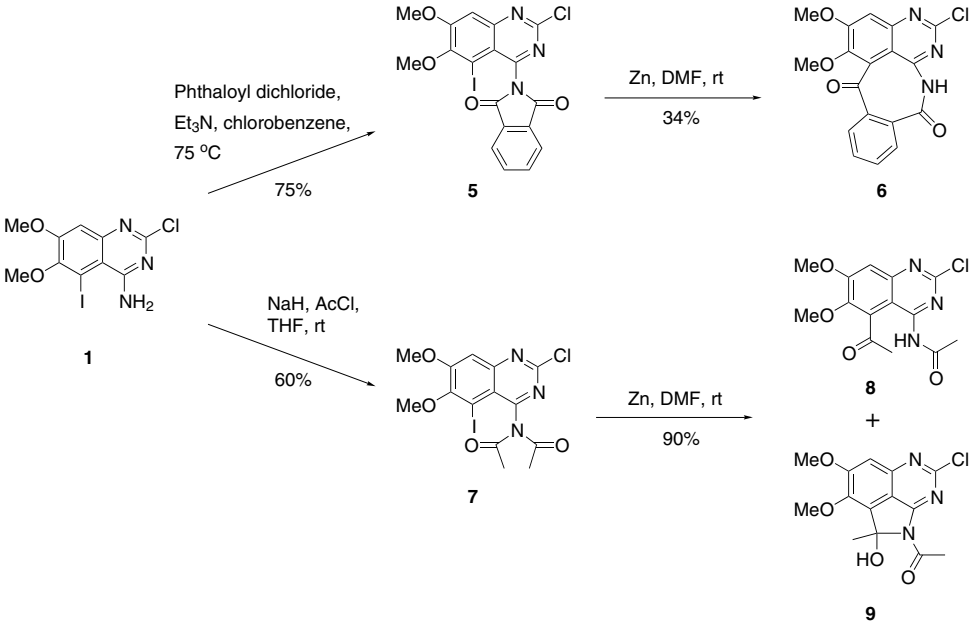
Therefore we investigated the possibility of inverting the nucleophilic and electrophilic partners in the reaction and employing the zinc reagent formed by iodine–metal exchange of **1**. The iodide **1** was treated with activated zinc in DMF,[11] followed by 2-iodopyridine and a palladium catalyst. Only the reduced compound **4** was produced. We reasoned that metallation of the iodide **1** had occurred, but that due to the proximity of the acidic N–H protons, intramolecular protonation of the organozinc intermediate had occurred, giving rise to the observed reduced product **4**.

To prevent quenching of the zinc reagent, we protected the free NH_2 group as a phthalimide (Scheme 3), a group previously used to protect amino groups in organozinc reagents.[12] To our surprise, on treatment of **5** with activated zinc at room temperature, the iodide underwent not reductive de-iodination as with the unprotected amine **1**, but smooth conversion to the 8-membered lactam **6**, the product of migration of one of the phthalimide carbonyls to the iodine-bearing carbon, presumably by nucleophilic attack of the intermediate organozinc reagent in a Barbier-like reaction.[13] This reaction was remarkably facile in occurring at room temperature. We attempted to capture the presumed intermediate organozinc species by addition of 2-iodopyridine, palladium acetate and triphenylphosphine, but the lactam **6** was the only product. The low yield (34%) appears to reflect the difficulty in isolation of the sparingly soluble product rather than the occurrence of side reactions. The *N*-diacetyl compound **7** underwent an analogous reaction, giving rise to the methyl ketone **8**. This compound exists, in $CDCl_3$, as a 3:1 mixture of cyclic hemi-aminal **9** and ketone **8** species.

It was clear the use of carbonyl-based *N*-protecting groups was unlikely to allow formation of a stable organozinc halide. Nevertheless, the acyl migration reaction was a synthetically interesting transformation. The migration of functionalized acyl groups was also successful (Scheme 4). Starting with the imide **10**, after zinc-mediated migration of one of the 5-benzoyloxyvaleryl groups, the benzoyl and remaining *N*-acyl groups were cleaved with methanolic potassium carbonate to



Scheme 4. Migration of functionalized acyl group.



Scheme 3. Zinc-mediated acyl migration reactions of quinazoline **1**.