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Tetrahedron Letters 46 (2005) 983–986
Tetrahedron Letters

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

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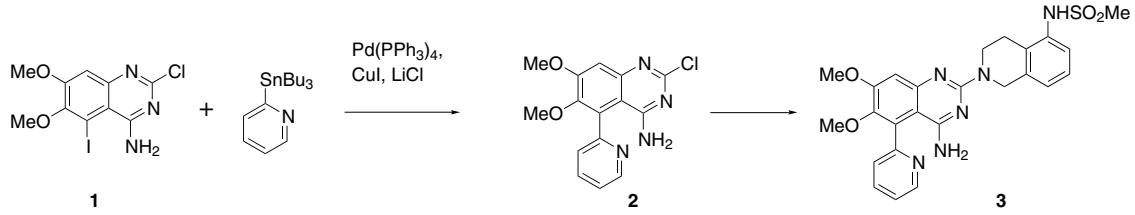
Received 13 October 2004; revised 19 November 2004; accepted 8 December 2004

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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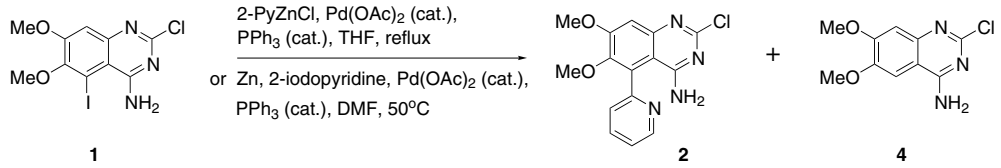
doi:10.1016/j.tetlet.2004.12.034

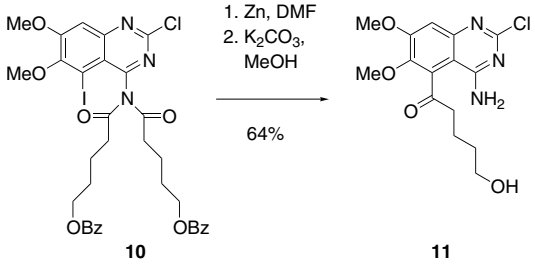


Scheme 2. Negishi couplings of iodide **1**.

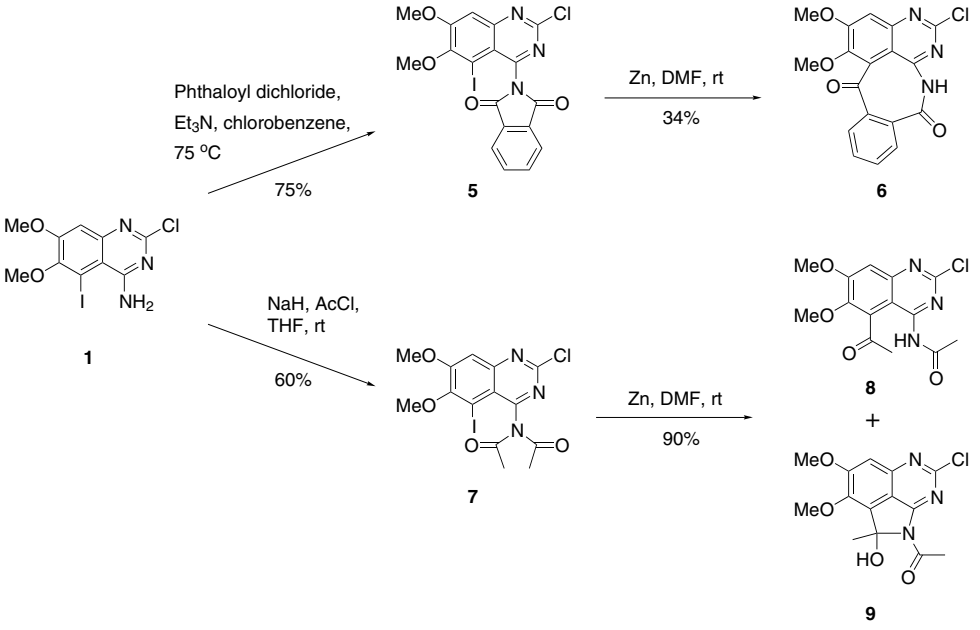
Therefore we investigated the possibility of inverting the nucleophilic and electrophilic partners in the reaction and employing the zinc reagent formed by iodine–metal exchange of **1**. The iodide **1** was treated with activated zinc in DMF,[11] followed by 2-iodopyridine and a palladium catalyst. 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.

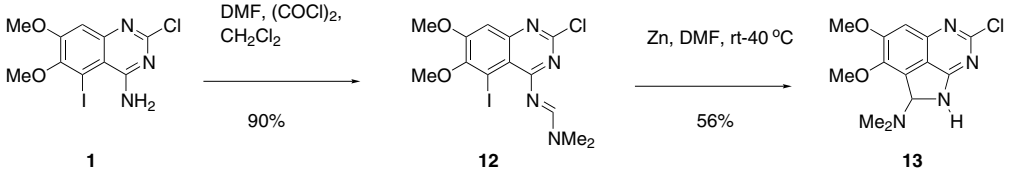
It was clear the use of carbonyl-based *N*-protecting groups was unlikely to allow formation of a stable organozinc halide. Nevertheless, the acyl migration reaction was a synthetically interesting transformation. The migration of functionalized acyl groups was also successful (Scheme 4). Starting with 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**.



Scheme 5. Zinc-mediated transfer reaction of formamidine **12**.

give the 5-hydroxyvaleryl ketone **11**. The intermolecular version of the acyl transfer reaction would also be of interest, but would not provide a solution to the current problem and was not investigated. In the search for alternative *N*-protecting groups, we tried a formamidine (Scheme 5).[14–17] Treatment of the iodide **12** with activated zinc led to the corresponding C–C bond-forming reaction with the amidine carbon, to give the cyclic aminal **13**, a derivative of the 5-formylquinazoline.

The preceding examples suggested that the N–C transfer reaction in this system was likely to be a general process. Therefore we decided to attempt to employ this method for introduction of the desired 2-pyridyl group. In order to prepare a suitable precursor **16**, coupling of the 2-pyridyl group to the amino group of **1** was required. However, we had previously found the amino group of **1** to be only weakly nucleophilic, requiring forcing reaction conditions to achieve acetylation for example. We attempted to couple this group by reaction of the aminoquinazoline **1** with 2-fluoropyridine using sodium hydride as a base. However, no reaction took place at room temperature, and on heating, de-iodination took place. Since aromatic nucleophilic substitution required conditions too forcing for the iodide to tolerate, and the alternative of a palladium-catalyzed coupling was also likely to be incompatible with this functionality, we adopted a more circuitous route in which the nucleophilic and electrophilic partners were inverted (Scheme 6). The 4-aminoquinazoline **1** was converted to the dichloride **14** using a modified Sandmeyer reaction.[18] Chlorination was accompanied by formation of the 4-quinazolone **15**. The crude product mixture was reacted with phosphoryl chloride to convert the quinazolone **15** to the dichloride **14**. Reaction of the dichloride **14** with 2-aminopyridine was selective for substitution at the 4-position, thus providing the required aminopyridine **16**. In order to effect pyridyl transfer, activation of the 2-aminopyridine **16** to an imino species analogous to the formamidine **12** was required. This was achieved by *N*-acylation of the pyridine. Reaction of the 2-aminopyridine **16** with di-*tert*-butyl dicarbonate led to the formation of the bright yellow pyridimine **17**. Isolation of the Boc pyridimine **17** was not possible, but the compound was stable for hours in solution at room temperature, allowing its identity to be confirmed by NMR.[19] On storage, the pyridimine **17** rearranges to the *N*-Boc aminopyridine **18** (Fig. 1). When acetic anhydride or

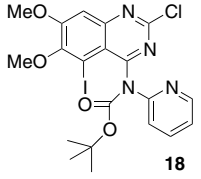
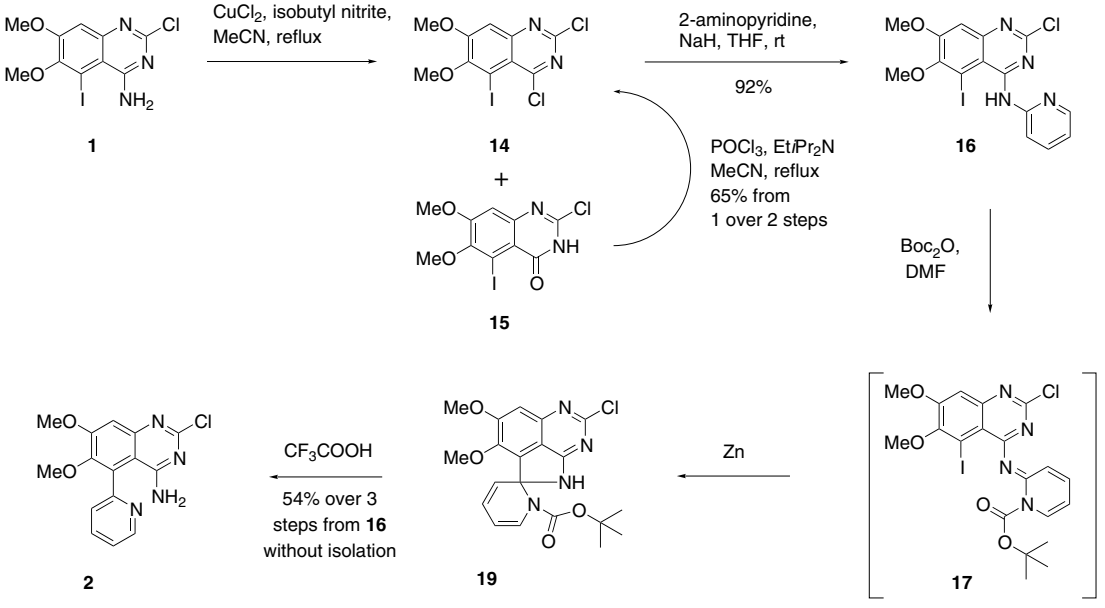


Figure 1. Rearrangement product of pyridimine **17**.



Scheme 6. Zinc-mediated pyridyl transfer.

tosyl chloride were used instead of di-*tert*-butyl dicarbonate, a yellow colour also resulted, signifying formation of the corresponding pyridimines, but these were much less stable than the *N*-Boc species **17**.

We were pleased to find that on addition of a preformed solution of the *N*-Boc pyridimine **17** in DMF to a suspension of zinc in DMF pre-activated with trimethylsilyl chloride and 1,2-dibromoethane that smooth migration of the pyridyl group occurred to give the spirocyclic dihydropyridine **19**. Upon treatment with trifluoroacetic acid, the spirocycle **19** collapsed to the desired pyridine **2**. The steps from the 2-aminopyridine **17** could be carried out without purification of the spirocycle **19**, giving the pyridine **2** in 54% overall yield. Thus, we were able to achieve introduction of a variety of acyl substituents and a 2-pyridyl group to the 5-position of the quinazoline **1**. We believe that the transfer reaction represents a valuable method for introduction of a range of substituents into sterically crowded and highly functionalized aryl systems.

Acknowledgements

This work was carried out in collaboration with Pfizer UK Ltd, Chemical Research and Development, Sandwich, Kent, CT13 9NJ, UK.

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