Late-Stage Sequential C-H Functionalization of Thiazolo[5,4-*f*]quinazolin-9(8*H*)-one: Synthesis of a Library of Potential Kinase Inhibitors

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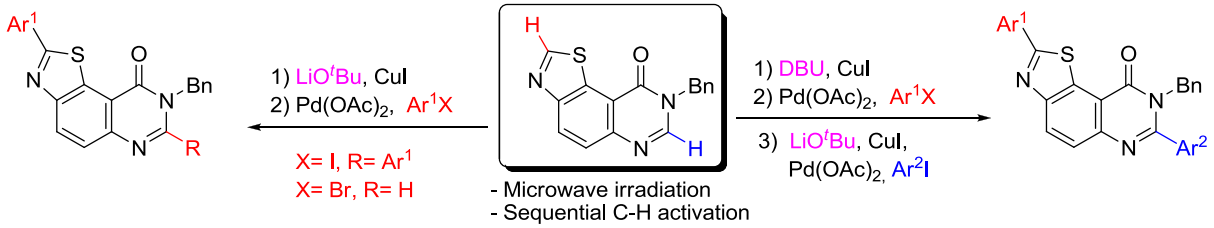
Abstract:

Mono- and bis-(hetero)-arylation of thiazolo[5,4-*f*]quinazolin-9(8*H*)-one backbone involving sequential activation of C-H bonds has been developed to furnish the corresponding mono- or diarylated valuable scaffolds. This strategy allows the regioselective C2-H and C7-H arylation by a judicious choice of coupling partners and bases. Differently substituted N^8-benzylated-2,7-diaryl-thiazoloquinazolin-9(8*H*)-ones were thereby obtained in a facile manner. A one-pot procedure was also developed. These protocols provide a synthetically useful route for late-stage functionalization of this high valuable scaffold, required in drug discovery.



Keywords: Thiazoloquinazolinone; C-H arylation; Microwave irradiation; Kinases inhibition; Alzheimer's disease.

1- Introduction

Our research group was focused on the synthesis of libraries of thiazolo[5,4-*f*]quinazolin(on)es as potential kinase inhibitors involved to some extent in Alzheimer's disease.[1] We previously reported that 9-*N*-alkylated/arylated thiazolo[5,4-*f*]quinazolines (II) displayed single-digit nanomolar IC_{50} values and are among the most potent DYRK1A/1B inhibitors disclosed to date.[2] Following our effort for the construction of an array of substituted thiazoloquinazolin-4-one derivatives,[3] the synthesis of an array of C2 and/or C7 arylated compounds was further envisioned (Figure 1). In this context, transition-metal-catalyzed C-C coupling of heteroarene through C-H arylation represents an extremely attractive approach, notably for the late-stage functionalization.[4] This methodology has emerged as an important tool for incorporating structural diversity into complex nitrogen containing heterocycles, without the need for prefunctionalized starting materials, useful in drug discovery.[5] Since high temperature and long reaction time are often required for the C-H activation, the microwave irradiation appears to be a suitable tool.[6]

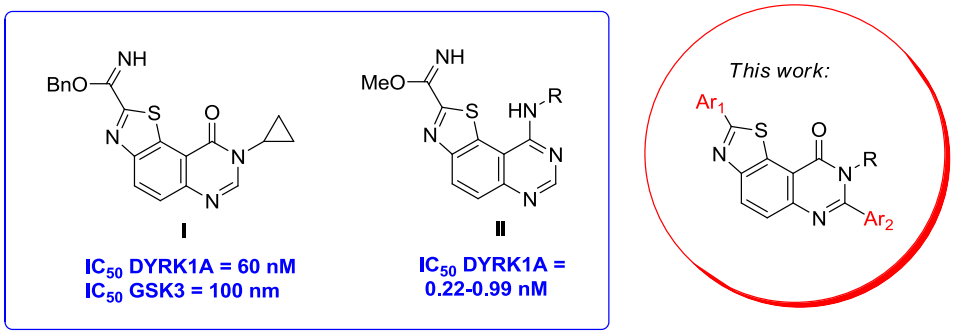
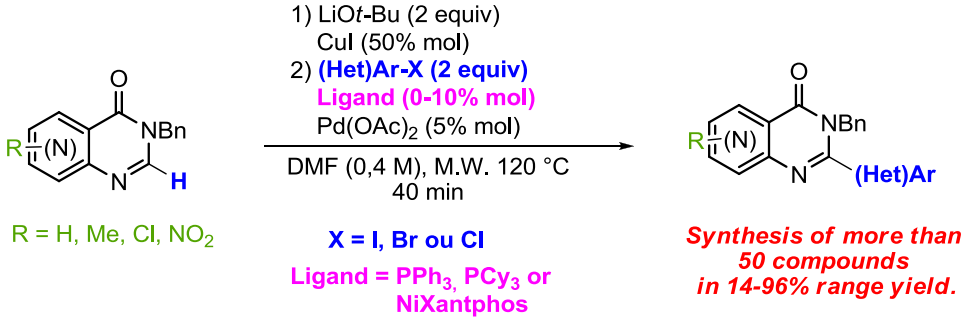
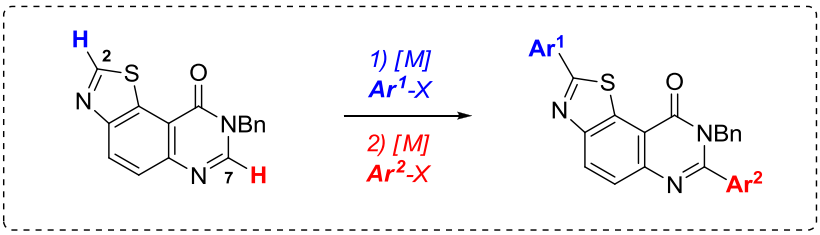


Figure 1. Structures of molecule hits and perspectives

Following our previous study on C-H arylation of quinazolinone skeleton as model substrate (Scheme 1),[7] a selective palladium-catalyzed and copper-assisted direct C-H (hetero)-arylation of thiazolo[5,4-*f*]quinazolin-9(8*H*)-one was envisioned with aryl halides as coupling partners under microwave irradiation (Scheme 2).



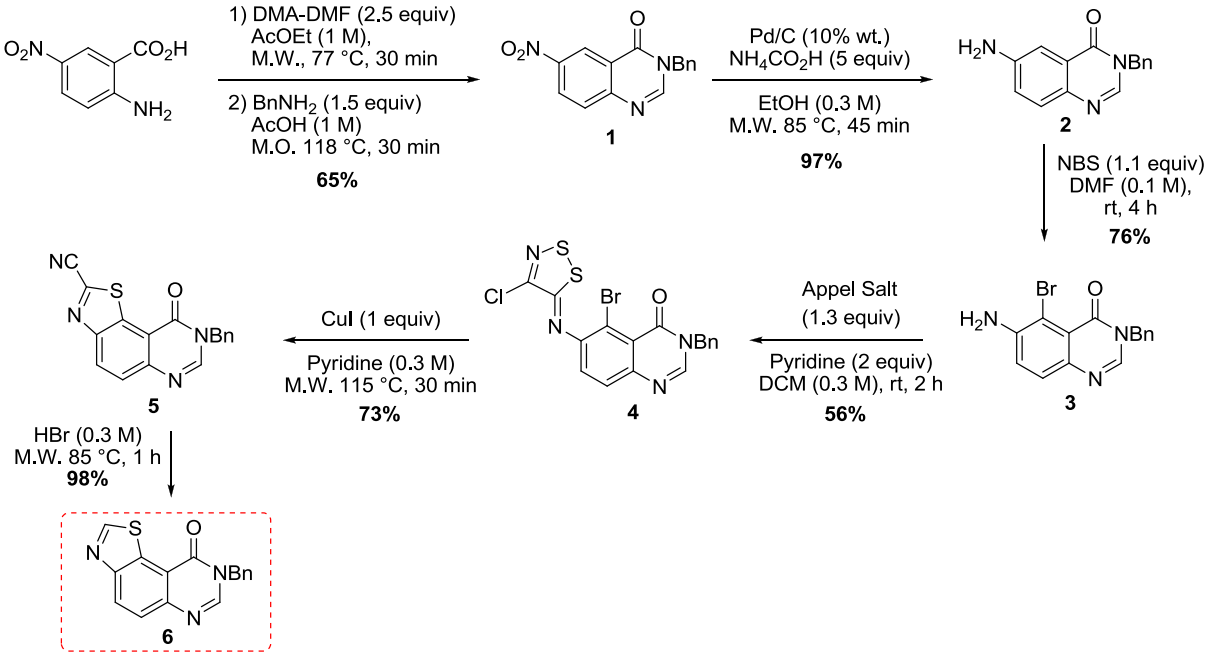
Scheme 1. Microwave-assisted C-H arylation of Quinazolin-4-one-type precursors of bioactive heterocycles: rapid access to biologically relevant *2*-arylquinazolin-4-one derivatives



Scheme 2. Late-stage functionalization's strategy through a metal catalysed C-H activation

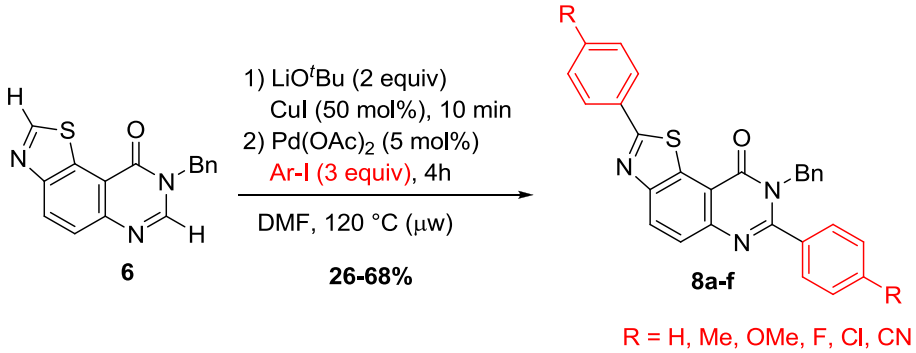
2- Results and discussion

Owing to the importance of DYRK1A inhibitors, structure-activity relationship (SAR) studies were considered. Among the potential chemical transformation, C2 and C7 functionalization of thiazolo[5,4-*f*]quinazolin-9(8*H*)-one core was investigated. In this context, transition metal-catalyzed intermolecular C-C coupling of this valuable scaffold through direct C-H arylation represents an extremely attractive approach, circumventing tedious multi-step syntheses in SAR studies. Given that selective C-H arylation is an ideal strategy for late-stage functionalization, we opted to use the N^8-benzylated-thiazolo-quinazolin-9(8*H*)-one **6** as the model substrate (Scheme 3), a unique scaffold and key structural unit in DYRK1 kinase inhibitor series.



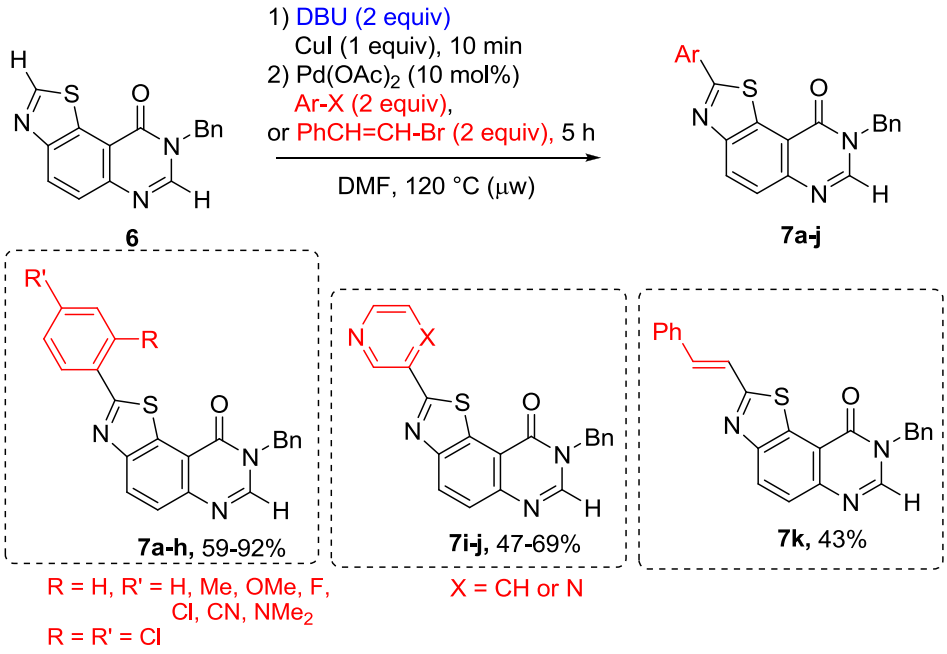
Scheme 3. Synthesis of N^8-benzylated-thiazolo-quinazolin-9(8*H*)-one 6 starting from 5-nitro anthranilic acid (6 steps, 19% yield)

When the reaction was conducted under our reported conditions on C2-H arylation of quinazolin-4-ones and pyridopyrimidin-ones,[7] a mixture of C2-mono- and C2/C7-bis-phenylated products **7** and **8** respectively was obtained. Increased loading of aryl iodide and longer reaction time afforded the bis-phenylated compound **8** in up to 68% yield.[8] With acceptable conditions established, the scope of the bis-arylation reaction was explored with aryl iodides (Scheme 4). When aryl iodide was introduced, the resulting 2-aryl-thiazolo[5,4-*f*]quinazolin-9(8*H*)-ones were reactive enough to perform a second arylation, yielding significant amounts of 2,7-bis-arylated products **8a-f**.



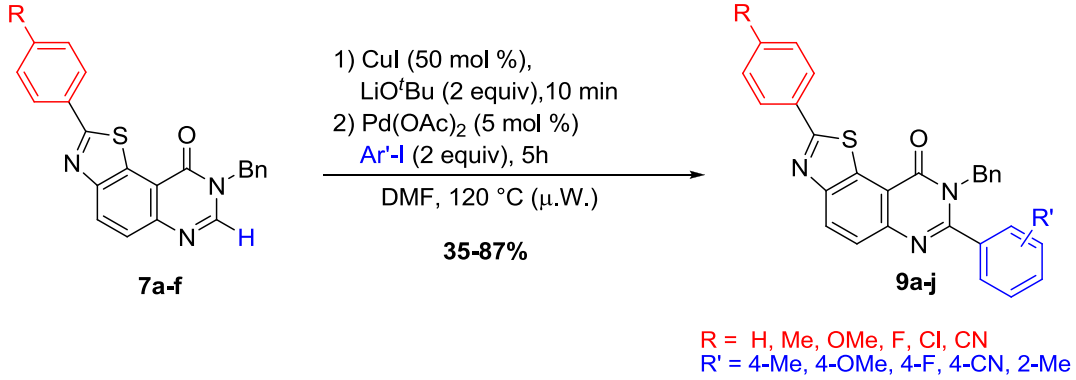
Scheme 4. Scope of the bis-arylation reaction

Since only *t*BuOLi was effective for the C-H arylation of quinazolin-4-one part,[7a] the selective C2-H arylation of the azole moiety has been achieved by switching the base. Indeed the reaction efficiency was dramatically improved by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the presence of 1.0 equiv of CuI.[8] Longer reaction time and 10 mol% $Pd(OAc)_2$ are also required for a total conversion of **6**. Under these conditions, both aryl iodides and bromides are effective as coupling partners to afford exclusively C2-arylated compound **7a-j** in a 47-92% range yield (Scheme 5). β-Bromostyrene was also an effective coupling partner as demonstrated by the alkenylation reaction leading exclusively to the corresponding (*E*)-isomer in 43% yield.



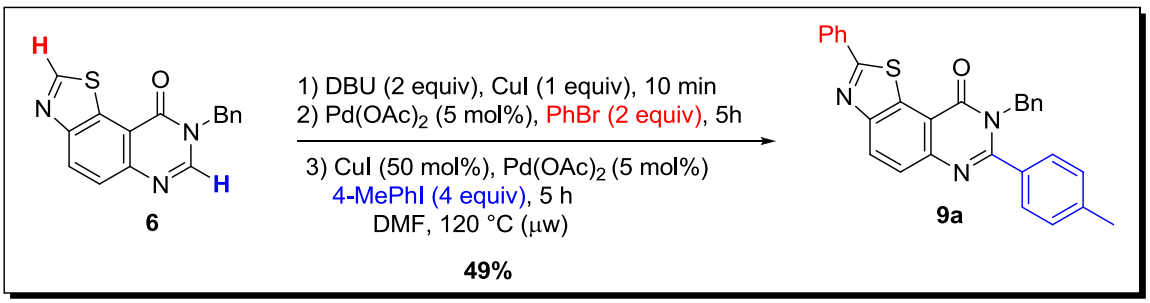
Scheme 5. Scope of the selective C2-H arylation reactions and alkenylation

The sequential C7-H arylation of compounds **7a-f** was performed using our previously reported conditions for C-H arylation of quinazolinones[7a] to afford the corresponding diarylated compounds **9a-j** in 33-87% yield after 5h (Scheme 6).



Scheme 6. Scope of the C7-H arylation reaction: Synthesis of diarylated compounds

The dual C-H bond functionalization was peformed in a one-pot process, allowing the chromatographic purification step discarded. The first C2-H arylation of **6** with phenyl bromide was complete within 5h, while the second arylation was finally achieved by the *in situ* addition of tolyl iodide, CuI (50 mol%) and $Pd(OAc)_2$ (5 mol%) to the mixture reaction. The expected C2 and C7 di-arylated thiazolo[5,4-*f*]quinazolin-9(8*H*)-one **9a** was isolated in acceptable yield (Scheme 7).



Scheme 7. Ligand Free One-Pot Sequential C2 and C7 Arylation of 6

3- Conclusion

This innovative sequential C-H functionalization tolerates a broad range of heteroaryl and aryl halides substituted by electronically different groups. Electron-deficient heteroarenes are also readily introduced at the C2 position, a notable feature with respect to medicinal agent synthesis Differently substituted N^8-benzylated-2,7-diaryl-thiazoloquinazolin-9(8*H*)-ones were thereby obtained in a facile manner. A one-pot procedure has also been performed. These protocols provide a synthetically useful route for late-stage functionalization of a high valuable scaffold, required in drug discovery. Brief studies of their Structure-Activity Relationships (SAR) as kinase inhibitors are currently under investigation.

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