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**PAPER**

# "On water" direct Pd-catalysed C–H arylation of thiazolo[5,4-*d*]pyrimidine derivatives†

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A novel protocol for the direct arylation of thiazolo[5,4-*d*]pyrimidine derivatives with aryl iodides is reported. The reactions were catalysed by a combination of $Pd(PPh_3)_4$ and $Ag_2CO_3$ (acting as the oxidant and the base as well), using exclusively water as the solvent and furnishing the desired products in good to excellent yields at only 60 °C.

## Introduction

2-Arylsubstituted thiazolo[5,4-*d*]pyrimidine derivatives are found to be the main motif of some pharmacologically relevant compounds such as Tie-2 inhibitors,[1a] phosphatidylinositide 3-kinases (PI3K) inhibitors,[1b] immunosuppressive agents,[1c] XOD inhibitor,[1d] human erythrocyte membrane phosphatidylinositol 4-kinase inhibitors[1e] and *E. coli* and *S. aureus* SecA inhibitors.[1f] Therefore, the synthesis of thiazolo[5,4-*d*]pyrimidine derivatives is a major concern in medicinal chemistry. Childress and McKee have achieved its synthesis by effective cyclization of benzoic anhydride with 5-amino-6-mercaptopyrimidine.[2] 2-Arylsubstituted thiazolo[5,4-*d*]pyrimidine derivatives can also be obtained through dehydrocyclization of 4-amino-5-arylamidopyrimidines with polyphosphoric acid or ring closure of benzoylaminopyrimidines with phosphorus pentasulfide.[3] These procedures require some toxic reagents and harsh conditions which have limited their applications. The direct construction of C–C bonds between 2-halo(bromine or chlorine) substituted thiazolo[5,4-*d*]-pyrimidine with phenylboronic acid or tributylphenylstannane catalyzed by palladium was also achieved.[1f] Although the advantages of the reactions include: (i) the easy realization of regioselectivity; (ii) the access to nearly all structural motifs due to thorough research of this area, they still suffer from the application of stoichiometric organometallic reagents together with troubles concerned with their preparations, stability and functional group compatibility.[4]

We report here a method for the coupling of thiazolo[5,4-*d*]-pyrimidine derivatives and aryl iodides with tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of silver carbonate in water. This method is representative of atom-economy.[5] Our procedure is one of the examples that uses water as a reaction medium rather than traditional organic solvents and is one of the few that can proceed at temperatures below 100 °C.[6] Therefore, it is a representative "on-water" reaction termed by Sharpless and co-workers.[7] Conducting the reaction on-water can be substantially benefits, such as safety because of its high heat capacity; the ease of operation and post-treatment due to the insolubility of both reaction substrates and products; most significantly it can greatly increase reaction rate and selectivity.[8] It should be pointed out that rate acceleration is not relevant to the amount of water used; it should just be enough to keep a clear phase separation.[9] The on-water procedure was first applied by Greaney and co-workers, viable to the direct arylation of several heteroarenes at temperature as low as 50 °C.[6a]

## Results and discussion

On the outset of our study, we tried to exam the direct coupling reaction between 7-chloro-2-methylthiazolo[5,4-*d*]pyrimidine **1** and iodobenzene **2a** in the presence of $Pd(dppf)Cl_2$, with $Ag_2CO_3$ and $PPh_3$ as base and ligand respectively, in water. Although 7-chloro-2-methylthiazolo[5,4-*d*]pyrimidine is nearly consumed, the yield was only 14%. After repeating several times, the results were still almost the same. Taking the hypothetical effect that $Ag^+$ may coordinate with chlorine in 7-chloro-2-methylthiazolo[5,4-*d*]pyrimidine and 7-chloro-5-methyl-2-phenylthiazolo[5,4-*d*]pyrimidine into consideration and with the expectation of higher yields, we substituted the substrate with 5-methyl-*N*-phenylthiazolo[5,4-*d*]pyrimidin-7-amine **3** (Scheme 1). Unfortunately, no reaction was detected between the substituted substrate and iodobenzene. According to the observation that none of substrate and desired product can be detected except iodobenzene, we speculated that the interaction between $Ag^+$ and the NH fragment may be responsible for this phenomenon. As we have noticed that free-NH[10] or $NH_2$ [11] are tolerated in the direct arylation between heteroarenes and aryl halides catalyzed by palladium, we can eliminate the effect of palladium. Besides, we are also aware of the fact that $Ag^+$ can crystallize with secondary amine and the formed complex has good solubility in polar solvents.[12] Compared with its counterpart, demethylated indole required a much longer reaction time, higher

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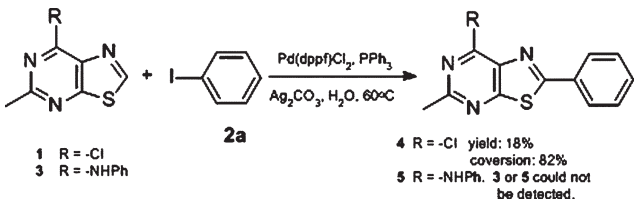
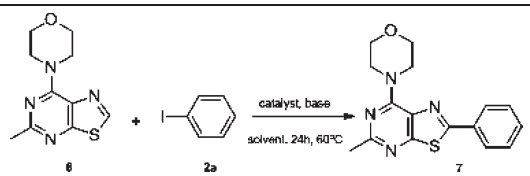
temperature and offered a lower yield in the direct arylation catalyzed by palladium and silver salt.[13]

Then, in order to continue our study, we used another substrate, 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine **6**, which can be obtained by the reaction between **1** and morpholine in ethanol at room temperature. The coupling reaction can be effectively carried out with 5 mmol% palladium-catalyst, in the presence of 10 mmol% $PPh_3$, using $Ag_2CO_3$ as the silver source and base, in water at 60 °C. $Pd(dppf)Cl_2$ and $Pd(PPh_3)_4$ can give the desired products in good yield (Table 1, entries 1, 3). However, the coupling with $Pd(OAc)_2$ as catalyst just offered a yield of 30% (Table 1, entry 2). From the angle of yield and cost, $Pd(PPh_3)_4$ is the favorable catalyst. Then, $Ag_2CO_3$ was replaced by $Cs_2CO_3$ or $K_3PO_4$. Unfortunately, the yields were trace or 8% respectively (Table 1, entries 4–5). Compared with entry 3, the yield of coupling was almost the same when $PPh_3$ was removed (Table 1, entry 6). Excellent yield was achieved when the amount of iodobenzene was increased to 2 equiv (Table 1, entry 7). Finally, the yield was drastically decreased after water was changed to acetonitrile (Table 1, entry 8). The good premixing of substrates and the catalytic system is vital to the success of the arylation reaction. It is an easy task for solid aryl halides, while enough attention should be paid to the liquid aryl halides. Solid components should be added first; then the liquid aryl halides, thus preventing them from adhering to the inner surface of microwave tube; last deionized water was injected. It should also be noted that the stirring bar may be strapped by the mixture which may induce incompletion of the reaction.



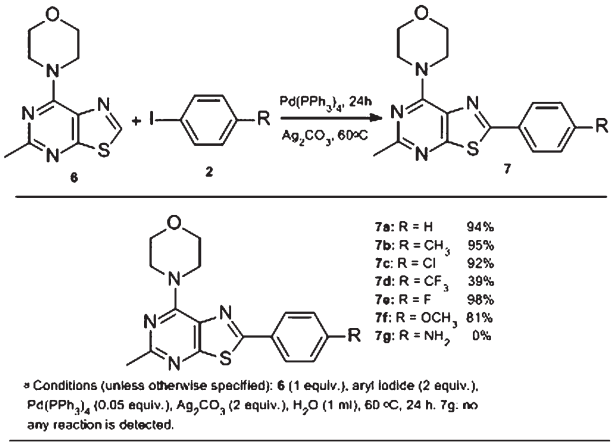

**Scheme 1** The direct arylation of 1 or 3 and iodobenzene.

**Table 1** Conditions screening for 4-(5-methylithiazolo[5,4-*d*]-pyrimidin-7-yl) morpholine **6** and iodobenzene[a]




| Entry | Cat. (equiv) | Base (equiv) | Solvent (ml) | Ligand (equiv) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Pd(dppf)Cl_2$ | $Ag_2CO_3$ | $H_2O$ | $PPh_3$ | 59 |
| 2 | $Pd(OAc)_2$ | $Ag_2CO_3$ | $H_2O$ | $PPh_3$ | 30 |
| 3 | $Pd(PPh_3)_4$ | $Ag_2CO_3$ | $H_2O$ | $PPh_3$ | 68 |
| 4 | $Pd(PPh_3)_4$ | $Cs_2CO_3$ | $H_2O$ | $PPh_3$ | Trace |
| 5 | $Pd(PPh_3)_4$ | $K_3PO_4$ | $H_2O$ | $PPh_3$ | 8 |
| 6 | $Pd(PPh_3)_4$ | $Ag_2CO_3$ | $H_2O$ | | 66 |
| 7[c] | $Pd(PPh_3)_4$ | $Ag_2CO_3$ | $H_2O$ | | 94 |
| 8[c] | $Pd(PPh_3)_4$ | $Ag_2CO_3$ | $CH_3CN$ | | 26 |

[a] Reaction conditions: **1** (0.1 mmol) and **2** (0.12 mmol), base (0.2 mmol), $PPh_3$ (0.01 mmol), catalyst (0.005 mmol), solvent (1 ml), 60 °C. [b] Isolated yield. [c] **2** (0.2 mmol). dppf = 1,1′-bis-(diphenylphosphino)ferrocene.

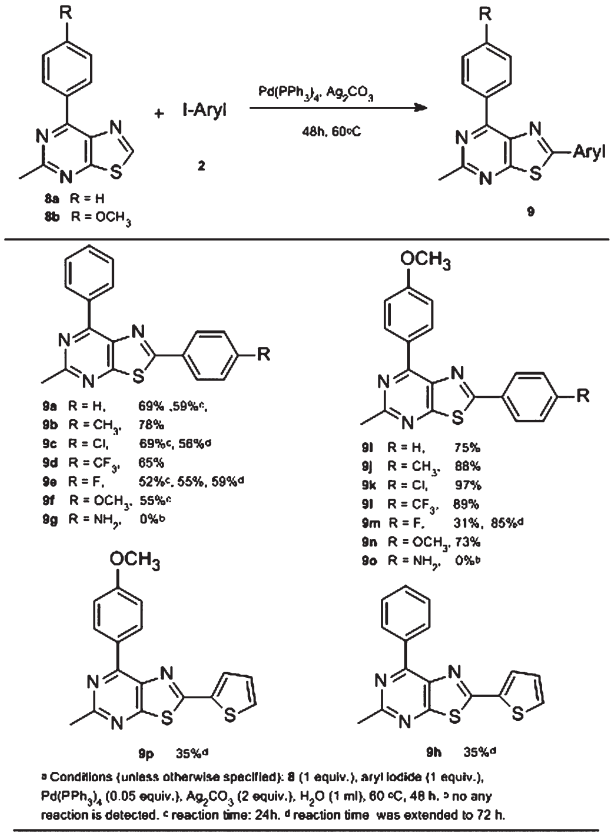



**Scheme 2** Pd-catalyzed C–H arylation between **6** and aryl iodides.

With this optimal catalytic system, the direct coupling reactions between 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)-morpholine **6** and several other aryl iodides were explored (Scheme 2). Aryl iodides bearing electron-donating functionalities offered the products in moderate to excellent yields (**7b**, **7f**). Unfortunately, *para*-iodoaniline failed to give any coupling product although it contains a strong electron-rich functionality (**7g**). The slightly electron-withdrawing groups furnished the desired products in good yields similar to that of electron-rich aryl iodides (**7c**, **7e**). However, this product can offer a platform for further elaboration as it contains chlorine (**7c**). Chlorine will not be a source of side reactions, because no reaction was detected between 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)-morpholine and chlorobenzene under this very catalytic system. The strong electron-withdrawing group, $–CF_3$, drastically decreased the yield, it offered the expected product **7d** in 39% yield.

It is also remarkable that the reaction between iodobenzene and more rigid 5-methyl-7-phenylthiazolo[5,4-*d*]pyrimidine **8a** proceeded efficiently under similar conditions, only requiring an extended reaction time of 48 h (Scheme 3, **9a**). Compared with 4-(5-methylthiazolo[5,4-*d*]-pyrimidin-7-yl)morpholine, the rigidity may be responsible for the longer reaction time. However, 7-(4-methoxyphenyl)-5-methylthiazolo[5,4-*d*]pyrimidine **8b** offered a higher yield than 5-methyl-7-phenylthiazolo[5,4-*d*]-pyrimidine, which may be due to the effect of the $OCH_3$ group, in which the oxygen may promote the combination of catalyst and substrate (**9i**). The electron-rich substitutes still contributed to the higher yields (**9b**, **9f**, **9j**, **9n**), while 4-iodoaniline gave no coupling product (**9j**, **9o**). Considering all the results of the reactions involving substrates bearing NH or $NH_2$ groups, we may conclude that this established catalytic system is not viable for them. Fortunately, the coupling reaction between 5-methyl-7-phenylthiazolo[5,4-*d*]pyrimidine derivatives with 2-iodothiophene is viable, although reaction times had to be prolonged to 72 h and the expected products were obtained in 34% and 35% yields




**Scheme 3** Pd-catalyzed C–H arylation between **8** and aryl iodides.[a]

respectively (**9p**, **9h**). The aryl iodides containing electron-withdrawing functionalities can give good to excellent yields (**9c**, **9e**, **9k**, **9m**). Even the reagents bearing strong electron-withdrawing $CF_3$ groups can still furnish products in 65% and 89% yields respectively (**9d**, **9l**).

## Conclusion

In conclusion, we have developed an effective and relatively inexpensive palladium catalytic system for the direct arylation of thiazolo[5,4-*d*]pyrimidine derivatives with aryl iodides using water as reaction medium. Furthermore, the reaction temperature is much lower than that of commonly reported in the literature in the direct arylation of heteroarenes catalyzed by transition metals. Further elaboration may be expected to enlarge the scope of functional group tolerance of this procedure.

## Experimental

### General

$^1H$ and $^{13}C$ NMR are recorded on 300 MHz spectrometers at 25 °C unless otherwise stated and are calibrated to residual solvent peaks ($CDCl_3$ 7.26, DMSO-$d_6$ 2.5, 3.3 ppm). The data is reported as chemical shift (ppm), and then the interpretation of the peak with relevant coupling constants reported in Hertz. $Pd(PPh_3)_4$ was stored in a refrigerator. Reactions were performed in a 10 ml microwave tube. 5-Methyl-*N*-phenylthiazolo[5,4-*d*]-pyrimidin-7-amine, 5-methyl-7-phenylthiazolo[5,4-*d*]pyrimidine, 7-(4-methoxyphenyl)-5-methylthiazolo[5,4-*d*]pyrimidine were synthesized according to the literature procedure.[14]

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