Synthesis of 2-Amino-5-arylthiazoles by Palladium-Catalyzed Arylation at the C5 Position with Aryl Iodides

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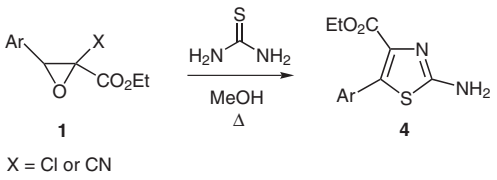
Received 21 May 2007

Abstract: A new synthetic route to afford 2-amino-5-aryl thiazoles has been developed. The starting aminothiazole derivative can be arylated at position 5 with aryl iodides under palladium-catalyzed conditions. Mechanistic studies suggest a proton-abstraction pathway for this transformation.

Key words: palladium, catalysis, cross-coupling, heterocycles, Heck reaction

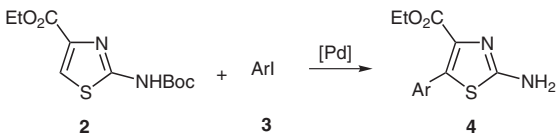
Aryl-substituted thiazoles have not only shown pharmacological activities,[1] but are also important as organic materials such as fluorescent dyes[2] and liquid crystals.[3] Usually, catalytic methods to prepare aryl heterocycles involve transition-metal-catalyzed coupling between an organometallic element and an aryl halide.[4]

More recently, as a major challenge in organic synthesis, significant attention has been given to the direct arylation of heteroarenes (without prior functionalization via metalation), achieved via cross-coupling of heteroaromatic sp^2 C–H bonds and aryl halides.[5]



Scheme 1

To the best of our knowledge, the only method described in the literature to obtain 2-aminothiazoles **4** consists of the reaction between the corresponding chloro/cyanoglycidate ester **1** and thiourea[6] (Scheme 1). The glycidate ester **1**, commonly prepared in two steps from the corresponding aryl aldehyde, is not very reactive and the final yields of these reactions are only moderate.

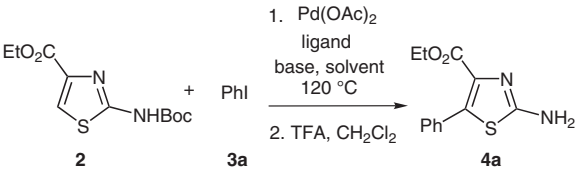


Scheme 2

SYNLETT 2007, No. 19, pp 2957–2960
Advanced online publication: 08.11.2007
DOI: 10.1055/s-2007-992368; Art ID: D15507ST

Herein, we describe a novel strategy for the synthesis of **4** based on Pd-catalyzed arylation at the C5 position of compound **2** (Scheme 2). The direct arylation of 2-aminothiazoles has not been reported to date.[7] Nonetheless, related studies in other heterocyclic systems, such as thiophenes, imidazopyrimidines, indolizines, furans and indoles are described in the literature.[8]

Table 1 Pd-Catalyzed Reaction of Thiazole **2** with Iodobenzene[a]



Entry	Ligand	Base	Solvent	Yield (%)[b]
1	PPh_3	Cs_2CO_3	DMF	11[c]
2	**5**	Cs_2CO_3	DMF	68
3	**6**	Cs_2CO_3	DMF	72
4	**7**	Cs_2CO_3	DMF	80
5	**7**	K_3PO_4	DMF	–
6	**7**	K_2CO_3	DMF	10[c]
7	**7**	Na_2CO_3	DMF	–
8	**7**	KOAc	DMF	–
9	**7**	Cs_2CO_3	THF	33[c]
10	**7**	Cs_2CO_3	MeCN	23[c]
11	**7**	Cs_2CO_3	toluene	–
12	**7**	Cs_2CO_3	dioxane	31[c]

[a] Reaction conditions: (1) $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), base (2 equiv), iodobenzene (1.5 equiv) in the corresponding solvent at 120 °C, 24 h; (2) TFA, CH_2Cl_2.
[b] Isolated yields.
[c] LC-MS yield.

Initial attempts to perform the metal-catalyzed cross-coupling reaction between iodobenzene and protected 2-aminothiazole **2**[9] were carried out under the standard conditions employed by Miura et al.,[7b] and only 11% yield of **4a** was achieved (entry 1, Table 1). After this promising result, optimization was carried out to find favorable conditions for the Pd cross-coupling reaction with aryl io-

dides. The study was executed taking iodobenzene as the standard aryl iodide to react with thiazole derivative **2**. The influence of the ligand, base and solvent was investigated (Table 1), and in addition to optimizing the reaction yield, provided valuable information about the likely mechanism.

The biphenyl phosphine ligands, such as **5**, **6**, or **7** (Figure 1), were the most appropriate ligands to carry out the Pd coupling reaction, affording the desired product **4a** in good yields[10] (entries 2–4, Table 1). The choice of the base was very important for this reaction, and only Cs_2CO_3 gave the coupling product with acceptable yield[11] (entries 4–8, Table 1). The solvent also plays a crucial role, DMF being the best for good conversions (entries 4, 9–12, Table 1), while nonpolar solvents are not suitable.

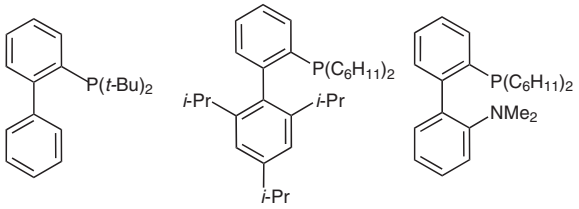


Figure 1 Biphenyl phosphino ligands

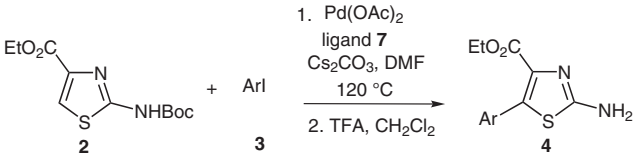
Once the optimal conditions for the coupling reaction between iodobenzene and thiazole derivative **2** had been found (entry 4, Table 1), the scope of this reaction was explored with a set of electronically and structurally diverse aryl iodides.[12]

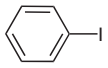
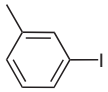
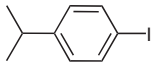
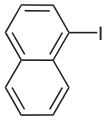
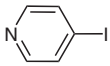
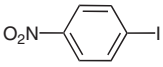
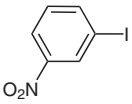
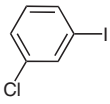
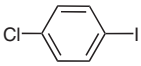
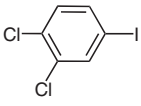
As can be seen in Table 2, thiazole **2** can be effectively arylated with different aryl iodides in moderate to good yields. As shown, a variety of substituents are tolerated in *meta* and *para* positions; substituents in *ortho* positions are also tolerated, however, these results are not shown here for reasons of compound legal protection. Substrates with electron-donating and some substrates with electron-withdrawing substituents show similar behaviors, leading to good yields of products (entries 2, 3 and 8–10, respectively). On the other hand, other electron-poor aryl iodides provide more moderate yields (entries 5–7).

The mechanism of this reaction could be explained in terms of three alternative routes, involving the structures shown in Figure 2. While none of these mechanistic possibilities can be definitively ruled out, we sought to determine which might be the most probable of the three. One possibility would be a Heck-like pathway,[13] where an insertion into the heterocycle would give an intermediate **8** and the corresponding arylated product **4** would then be obtained after a *trans*-β-hydrogen elimination. We believe that on balance this mechanism is less probable than the other two.

An electrophilic aromatic substitution pathway (intermediate **10**) has often been considered as the most probable mechanism for arylation of heterocycles.[14] Following the

Table 2 Pd-Catalyzed Arylation of Thiazole **2**[a]



Entry	ArI	Yield (%)[b]
1		**4a** (80)
2		**4b** (76)
3		**4c** (90)
4		**4d** (87)
5		**4e** (40)
6		**4f** (48)
7		**4g** (45)
8		**4h** (79)
9		**4i** (85)
10		**4j** (75)

[a] Reactions conditions: (1) $Pd(OAc)_2$ (5 mol%), ligand **7** (10 mol%), base (2 equiv), iodobenzene (1.5 equiv) in DMF at 120 °C, 24 h; (2) TFA, CH_2Cl_2.
[b] Isolated yields.

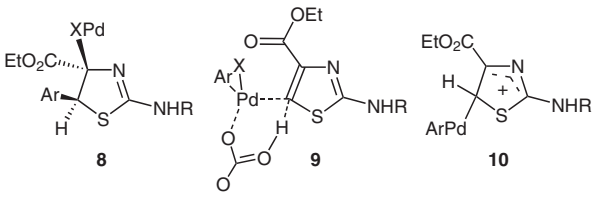


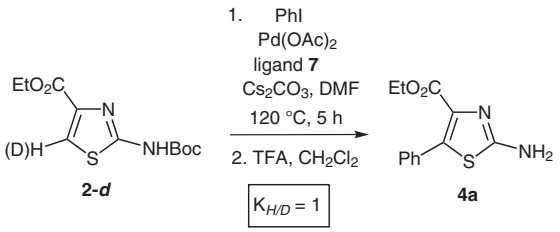
Figure 2 Possible intermediates for Pd-catalyzed arylation of thiazole

procedure used by Gevorgyan et al.[15] to support this proposed mechanism, we carried out a density functional theory (DFT)[16] geometry optimization calculation (B3LYP[17]/6-31G**) on the thiazole core of **2**. Although

this heterocycle has a HOMO (E_{HOMO} = –6.87 eV) that could participate in an electrophilic aromatic substitution reaction, it is not an electron-rich ring. The HOMO of this thiazole is 1.91 eV lower in energy than the HOMO of the reference indolizine described in the literature.[15] Partial charges derived from the same calculation were also notably more negative for the indolizine (–0.43) than for the thiazole (–0.28) at the reacting center. These observations disfavor but do not eliminate the possible involvement of this pathway.

The last of the proposed pathways is a mechanism in which Pd-catalyzed arylation involving a proton abstraction by a carbonate or related ligand could give a C3-arylated transition state **9**; this mechanism (which is also consistent with our observations in Table 1) is similar to that recently proposed by Echavarren, Maseras et al.[18] for a related intramolecular direct arylation reaction.[19] If a proton-abstraction pathway involved proton transfer as the rate-determining step, a kinetic isotope effect (KIE) should be seen and a study was performed in the arylation of thiazole **2-*d*** with iodobenzene (Scheme 3).

No KIE ($K_{H/D}$ = 1) was detected in a competition experiment when a mixture of **2** and **2-*d*** was subjected to standard arylation conditions and stopped at 50% conversion. This result does not exclude this mechanism; lack of a KIE could be due to turnover-limiting oxidative addition, which occurs before the proton-abstraction step.[20]



Scheme 3 Isotope-effect study

We therefore undertook another DFT study, to see whether the calculated transition-state energy would be consistent with the idea that this Pd-catalyzed arylation reaction[21] could go via proton abstraction by carbonate instead of electrophilic aromatic substitution.[22] The DFT calculations employed the B3LYP functional on a model system where the phosphine ligand was modeled by PH_3, and the ester was replaced by a carboxylic acid on the thiazole ring to reduce computational cost. Initial coordinates were based on the transition state reported for a related system by Echavarren, Maseras et al.[18] The standard 6-31G** basis set was used for all atoms, except for palladium, which was described by the LACVP valence basis set. Geometries were fully optimized, without symmetry constraints, in the gas phase. A transition state was located from a linear transit scan in which the C–H bond length of the migrating hydrogen was kept fixed at various distances, while all other degrees of freedom were optimized. The transition state was then optimized using DFT quadratic synchronous transit.

The computed structures for reactant, transition state (only one negative frequency, corresponding to the desired proton transfer, is observed, at –915.22 cm^{-1}), and product are shown in Figure 3. The energy barrier is as low as 6.11 kcal/mol, a readily acceptable value for a reaction carried out at 120 °C and indeed one which would strongly suggest that this would not be the rate-determining step for the overall process. This value may be compared with 23.5 kcal/mol reported for the Pd-catalyzed intramolecular arylation described by Echavarren, Maseras et al.[18]

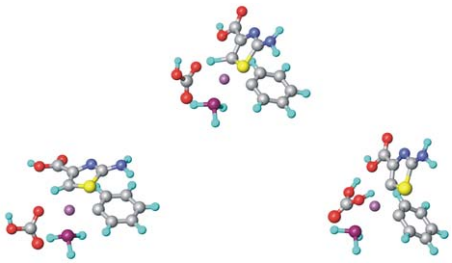


Figure 3 Reactant, transition state and product (left to right)

We therefore conducted a further experiment demonstrating significant rate enhancement in the presence of CuI (20 mol%), which has been suggested by Gevorgyan et al.[15] to strongly support the proton-abstraction mechanism.

In summary, direct Pd-catalyzed arylation at the C5 position of 2-aminothiazole **2** with different aryl iodides has been studied. This new methodology can be used to prepare 2-amino-5-aryl-substituted thiazoles in one step in moderate to good yields. While we cannot exclude any of the three mechanisms, our experimental and theoretical results suggest that the reaction probably goes through a proton-abstraction mechanism, in which the proton transfer itself is not the rate-determining step.

Acknowledgment

We thank Prof. Antonio M. Echavarren (ICIQ, Tarragona) for helpful comments, exchange of information and advice on the preparation of this manuscript; Prof. Erick M. Carreira (ETH, Zurich) for helpful suggestions and Cristina Anta (Analytical Technologies, Lilly, S. A.) for purification support.

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(12) **Typical Experimental Procedure**
A 16 × 100 tube was charged with thiazole **2** (0.37 mmol), aryl iodide (0.55 mmol), Cs_2CO_3 (0.239 g, 0.73 mmol), $Pd(OAc)_2$ (0.004 g, 5 mol%, 0.02 mmol), ligand **7** (0.014 g, 10 mol%, 0.04 mmol) and DMF (2 mL, 0.2 M). The resulting mixture was stirred at 120 °C for 24 h under a nitrogen atmosphere. The mixture was then filtered through Celite and concentrated to dryness. The residue was purified first on silica gel (4:1 hexane–EtOAc) and then with an HLB cartridge [using NH_4HCO_3 (pH 10) and MeCN as eluents]. Next, the compound was dissolved in CH_2CH_2 (1 mL) and TFA in CH_2CH_2 (25%, 1 mL) was added. The corresponding solution was shaken on an arm shaker overnight. After that, the mixture was concentrated to dryness, dissolved in MeOH, passed through an SCX-2 cartridge; two volumes of MeOH and two volumes of NH_3–MeOH (2 N) were eluted. The NH_3–MeOH washings were concentrated to dryness to afford the desired compound.
2-Amino-5-phenylthiazole-4-carboxylic acid ethyl ester (**4a**): white solid (73 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.38 (m, 5 H), 5.48–5.39 (m, 2 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 1.19 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.91, 160.92, 135.83, 134.10, 129.81, 129.02, 127.62, 126.99, 59.99, 13.02.
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