Palladium-catalyzed couplings to 7-azaindoles with formation of C-C bonds

Introduction

In recent years, compounds with the 1H-pyrrolo[2,3-b]pyridine moiety (more commonly named 7-azaindole; Mérour and Joseph, 2001) have been shown to display significant biological activities. Following these observations, the synthesis of variously substituted 7-azaindole derivatives has become a subject of major concern for medicinal chemists. As a continuation of our precedent review (AtlanChim newsletter N°3), we present herein known examples of palladium-catalyzed carbon-carbon bond formation at carbons C₂, C₃, C₄, C₅ and C₆ of the 7-azaindole nucleus.

NB : Patent literature is not included in this review.

1. Functionalization at carbon C₂

The first reported example was due to Mérour and coll. (1997) who succeeded in coupling the 2-(trimethylstannyl)-7-azaindole 2, prepared by lithiation of 1-phenylsulfonyl-7-azaindole 1 and subsequent quenching with trimethylstannylchloride, with two aromatic iodo derivatives. Interestingly, compound 3a, subjected to the conditions of the Bishler-Napiealski reaction, afforded the new heterocyclic pattern 4 in fair yield rather than the expected structure 5 (Scheme 1).

Scheme 1
Later on, a general study of the palladium-catalyzed coupling reaction of 3-substituted-2-iodo-7-azaindoles has been reported by Chi et al. (2000). Using 5% Pd(OAc)$_2$, LiCl and KOAc in DMF as standard conditions, aliphatic and aryl substituents could be successfully introduced at carbon C$_2$ by Suzuki-Miyaura, Stille and Heck reactions. Thus, the reaction of phenylboric acid with several 2-iodo-7-azaindoles provided the corresponding 2-phenyl-7-azaindoles in yields ranging from 60 to 86%. Allyl, vinyl and phenyl substituents were introduced in similar yields from the corresponding tin derivatives. Couplings of methylacrylate, methylvinylketone and but-3-en-2-ol (Heck reaction) were also effected with success. Scheme 2 provides with an illustration of each of these procedures.

\[
\begin{align*}
\text{Conditions :} & \quad 5\% \text{ Pd(OAc)}_2, 1 \text{ eq. LiCl, 2 eq. KOAc, DMF, 110° C.}
\end{align*}
\]

**Scheme 2**

Following their pioneering work, Mérour and coll. (2000) also reported the Stille coupling of the 1-phenylsulfonyl-iodo-7-azaindole 12 with vinyltributyltin to give 13 in good yield. Compound 12 also reacted with methylacrylate in the conditions of the Heck coupling to give 14 in fair yield. Compound 13 was subsequently shown to give Diels-Alder adducts in a complete regioselective manner.

\[
\begin{align*}
\text{Conditions :} & \quad \text{Bu$_3$Sn, Pd(PPh$_3$)$_4$, LiCl, DMF 90°C, 2h} \\
\text{Conditions :} & \quad \text{CO$_2$Me, Pd(OAc)$_2$, PPh$_3$, NEt$_3$, DMF 90°C, 3h}
\end{align*}
\]

**Scheme 3**

In the course of a medicinal effort aimed at finding new potent gonadotropin-releasing hormone (GnRH) antagonists, Ujjainwalla and Walsh (2002) reported the preparation of the 7-azaindole 17. The 2,4-dimethylphenyl substituent at carbon C$_2$ was introduced by recourse to an efficient Suzuki-Miyaura coupling as shown in Scheme 4 (15 $\rightarrow$ 16). Relatively to its indole analogue, 17 was
found to be a very potent GnRH antagonist. Following a very similar route, the 6-azaindole analogue was also synthesized. Its biological activity was not reported however.

\[
\begin{align*}
\text{MeO} & \quad \text{N} \\
\text{O} & \quad \text{Bn} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{N} \\
\text{O} & \quad \text{Bn} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{N} \\
\text{O} & \quad \text{Bn} \\
\end{align*}
\]

Scheme 4

2. Functionalization at carbon C\(_3\)

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{X (X = Sn, I)} \\
\end{align*}
\]

In a research program aimed at discovering analogues of neviparine 18, a non-nucleoside reverse transcriptase inhibitor, Kelly and coll. (1997) explored the effect of anchoring diversely substituted indole and azaindole rings at carbon C\(_3\) of a closely related neviparine skeleton. This was achieved, albeit in a very low yield, through the intermediacy of a Stille reaction as shown for compound 21 taken as an example (19 + 20 → 21, scheme 5). Note that 4-, 5- and 6-azaindolyl motifs were also coupled to 19 following an identical procedure.

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{X (X = Sn, I)} \\
\end{align*}
\]

Scheme 5

Two years later, Alvarez and coll. (1999) reported their results dealing with the preparation of 7-azaindoles substituted at carbon C\(_3\) with pyridin-2-yl and pyrimidin-5-yl moieties. A Stille reaction between the 1-protected 3-trimethylstannyl-7-azaindole 20 (R=TBDMS) and the appropriately chosen heteroaryl bromide was put into practice to reach the targeted compounds. It was shown that the nature of the protecting group at C\(_1\) of 20 (e.g. TBDMS, MEM, Boc, Ts) has a little influence on the yield of the reaction whereas the attachment of a pyrimidin-5-yl substituent is significantly more efficient than a pyridin-2-yl substituent (scheme 6, TBDMS is the protecting group).
Kuo and coll. (2003, 2004) reported the synthesis of macrocyclic maleimides exhibiting potent and selective inhibition towards glycogen synthase kinase-3β (GSK-3β), (e.g. 28). As shown in Scheme 7, a palladium-catalyzed Stille reaction between the 3-trimethylstannyl-7-azaindole 20 (R=Boc) and the chloroindolylmaleimide derivative 24, or the 2,3-dichloro-N-methylmaleimide 25, was effective to prepare the key synthetic intermediates 26 or 27, respectively.

Although not strictly relevant to this review we may cited herein examples of palladium-catalyzed heteroaryl coupling reactions of 5-halogeno-pyrido[3′,2′:4,5]pyrrolo[1,2-c]pyrimidine derivatives for the introduction of a pyrimidine substituent at C3 of the 7-azaindole moiety. These reactions were carried out in the context of the synthesis of the alkaloids of marine origin variolin and deoxyvariolin B, which exhibit cytotoxic activities against the P388 cell line next to being active against Herpes simplex. For example, in their synthesis of deoxyvariolin, Alvarez et al. (2001, 2003) described the Stille reaction between the 2-(methylthio)-4-(trimethylstannyl)pyrimidine and the iodo derivative 29 to give an advanced precursor (30) of the targeted molecule (Scheme 8). Other closely related examples can be found in recent work done by Molina (2002, 2003) and Vaquero (2004).
3. Functionalization at carbon C₄

Known examples of such a C-C coupling reaction are scarce. Arcadi and coll. (2001) described the reaction of 4-chloro-7-azaindole 31 with a series of aromatic and heteroaromatic boronic acids under conditions of the Suzuki coupling (e.g. 31 $\rightarrow$ 32). They also reported reactions of the 4-iodo-1-acetyl-7-azaindole 33 with 2-methyl-3-butyne-2-ol under conditions of the Sonogashira coupling to give compound 34 in up to 94% yield (Scheme 9). Examples of Heck coupling reactions were also reported in the same paper (Scheme 10). It is worth noting that the reaction course of the palladium acetate-catalyzed reaction of 33 with methyl acrylate is controlled by the nature of the base present in the reactional medium. Thus, if NEt₃ led to the formation of the C₄ coupling products 36a (38%) and 36b (45%, deprotected form), use of more basic conditions (e.g. K₂CO₃/KOAC) led, by contrast, to the Michael adduct 37 as the sole isolated compound (58%).
Scheme 10

Note that Thutewohl et al. (2006) recently reported the substitution of 4-chloro-7-azaindoles with anilines and arylphenols via palladium-catalyzed coupling reactions with formation of C-N and C-O bonds, respectively.

4. Functionalization at carbon C₅

\[(X = \text{Br})\]

In the search for new melatonine analogues, Viaud-Massuard and coll. (2003) developed a palladium-catalyzed method allowing the access to dimers of 7-azaindole. Thus, in situ formation of borane 40 from 5-bromo-1-methyl-7-azaindole 38 and tetraalkoxydiboron 39, followed by a Suzuki homocoupling reaction with 38, afforded the dimer 41 in good overall yield. Subsequent chemical transformations allowed the introduction of the N-ethylacetamide side chain also present in melatonin (→ 42, scheme 11).
The first known examples of such a transformation were reported by Ohshira and coll. (1992). Thus, palladium-catalyzed reaction of 6-bromo-7-azaindole 43a with trimethylsilylacetylene afforded the coupling product 44 which was subsequently desilylated and debenzoylated to give the 6-ethynyl-7-azaindole 45. Treatment of the more reactive 6-iodo-7-azaindole 43b with gaseous acetylene afforded, in the presence of the same catalytic system as above, the bis-coupling product 46, next N-deprotected into 47 by exposure to the action of a base (Scheme 12).
Scheme 12

In a paper mentioned above, Arcadi and coll. (2001) also reported examples of preparation of 6-substituted-7-azaindoles through palladium-mediated coupling reactions. Thus, in the presence of a palladium catalyst, the 6-chloro-7-azaindole 48a reacted with phenyl- and 2-furanyl-boronic acids to give the corresponding coupling products in 76 and 40% yields, respectively, whereas the 6-bromo-7-azaindole 48b was prone to Sonogashira and Heck couplings (Scheme 13).

Scheme 13

In the course of a total synthesis of the marine cytotoxic agent glossularine, Hibino and coll. (1995) reported the three-component Suzuki coupling reaction between tosylate 52 (embodying the 7-aza-indole skeleton), carbon monoxide and [4-(methoxymethoxy)-phenyl]boronic acid to provide the desired 2-benzoyl-pyrido[2,3-b]indole 53, albeit in low yield (19%), along with compound 54 (58%).
They also reported the preparation of methyl ester 55 from tosylate 52 in an excellent yield of 93% (Scheme 15). Further manipulations of 55 allowed the improvement of the synthesis of glossularine B and a synthesis of glossularine A.

A very similar approach to the analogs of glossularines A and B, lacking the dimethylamino group, was concomitantly reported by Achab et al. (1995) using Stille coupling reactions.

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References