Tetrahedron 72 (2016) 6711–6727

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report 1125

Functionalization of indazoles by means of transition metal-catalyzed cross-coupling reactions

Saïd El Kazzouli [a,*], Gérald Guillaumet [b,*]

[a] EuroMed Research Institute, Euro-Mediterranean University of Fes, Route de Meknes, 30000 Fes, Morocco
[b] Institut de Chimie Organique et Analytique (ICOA), Université d'Orléans, UMR CNRS 7311, BP 6759, Orléans Cedex, 2 45067, France

ARTICLE INFO

Article history:
Received 14 April 2016
Available online 24 August 2016

Keywords:
Indazole
Cross-coupling
Sonogashira
Heck
Suzuki–Miyaura
Stille
N-arylation
C–H activation
Direct arylation
Oxidative alkenylation

Contents

1. Introduction

The indazole system was found in various biologically active molecules. For very recent applications, indazole was reported as e.g., selective estrogen receptor degraders,[1] selective 5-HT2 receptor agonist,[2] anticancer agents mostly as kinase inhibitors,[3] inhibitors of Aurora A (kinase involved in cell cycle),[4] selective CRAF inhibitors,[5] FGFR inhibitors[6] as well as inhibitors of other kinases.[6–10] It was described also as bacterial gyrase B inhibitors[11] and as highly potent and selective human beta(3)-adrenergic receptor agonists.[12] Indazole is also present in various drugs and drug candidates including bendazac[13–15] (compound **I**), benzydamine[16] (compound **II**), pazopanib (Votrient®)[17] (compound **III**), granisetron (Kytril®)[18,19] (compound

* Corresponding authors. E-mail address: s.elkazzouli@ueuromed.org (S. El Kazzouli).

http://dx.doi.org/10.1016/j.tet.2016.08.031

IV) and gamendazole[20,21] (compound **V**) (Fig. 1). For more details on biological applications of indazoles, a very interesting review has been recently published.[22] Other relevant reviews focused on indazoles synthesis, properties and applications have also been reported.[23,24] However, none of these reviews has been dedicated to the results achieved in the field of metal-catalyzed cross-coupling reactions. In this review paper, we wish to discuss and summarize the advances made since 1999 in this field toward indazoles functionalization (e.g., Sonogashira, Heck, Suzuki–Miyaura, Stille, direct arylation, oxidative alkenylation, oxidative heteroarylation, N-arylation and sequential double functionalization). Procedures in which metal-based catalysis is not involved in the functionalization of indazoles are not included.

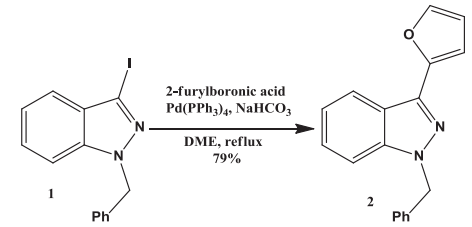
2. Functionalization by cross-coupling reactions

2.1. Suzuki

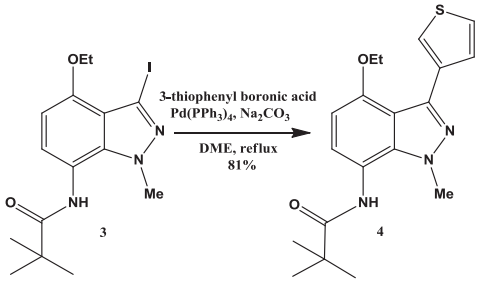
In 1999, Rault et al. reported the first example of Suzuki–Miyaura cross-coupling reaction toward the preparation of 3-arylindazoles.[25] The presence of the NH free group of 3-haloindazoles was a limiting factor, especially in the case of 3-bromoindazole. In contrast, when 3-iodoindazole **1**, protected by a benzyl group, was treated by 2-furylboronic acid, the expected product **2** was isolated in acceptable yield (79%). The reaction was conducted under the following conditions [1.1 equiv of 2-furylboronic acid, 5 mol % of $Pd(PPh_3)_4$, 3 equiv of $NaHCO_3$ in DME at reflux for 3 h] (Scheme 1). Authors showed that the use of NH free iodoindazole as starting material led to the expected products but in lower yields.

In 2005, our group prepared 3-heteroarylated indazole **4** by treatment of 3-iodo-1-methyl 4,7-disubstituted indazole **3** under standard Suzuki–Miyaura conditions [3-thiophenylboronic acid, $Pd(PPh_3)_4$ and Na_2CO_3 in refluxing DME].[26] This procedure led to desired 3,4,7 trisubstituted indazole **4** in 81% yield (Scheme 2).

In the same year, two other examples of C4-(hetero)arylated indazoles using Suzuki–Miyaura cross-coupling reaction have been synthesized. Both compounds were obtained in good yields after the treatment of 4-iodoindazole **5** by either 4-methoxyphenyl- or 3-thiophenylboronic acid in the presence of a catalytic amount of $Pd(PPh_3)_4$ and Na_2CO_3 in refluxing DME.[27] The desired products **6** and **7** were isolated in 85 and 80% yield, respectively (Scheme 3).



Scheme 1. The first example of Suzuki–Miyaura cross-coupling.



Scheme 2. Suzuki–Miyaura reaction on **4**, **7** disubstituted indazole **3**.

One year later, we applied Suzuki–Miyaura reaction for the synthesis of bioactive indazoles.[28] The starting materials **8** and **11** were treated under standard reaction conditions [1.1 equiv of *p*-MeO–C_6H_4–$B(OH)_2$, 5 mol % of $Pd(PPh_3)_4$, 3 equiv of $NaHCO_3$, DME at reflux for 3 h]. This procedure led to desired product **12** in good yield (Scheme 4). In contrast, we noticed that the reaction between **8** and *p*-methoxyphenyl boronic acid gave the desired product **9** in only 45% yield (36% of *N*-deprotected indazole **10** was isolated). The cleavage of the tosyl protecting group was observed under the basic conditions required for Suzuki–Miyaura coupling. This phenomenon was behind of the low yield observed for compound **9**.

In 2009, Rault and his group reported the synthesis of protected indazolylboronic esters and their applications in Suzuki–Miyaura cross-coupling.[29] So, in a representative example, starting from *N*-SEM 5-bromoindazole **13** and bis(pinacolato)diboron (1.15 equiv) in the presence of KOAc (4.6 equiv), $PdCl_2(dppf)$-CH_2Cl_2 (0.08 equiv) under argon, intermediate **14** was obtained in 67% yield. Then, the treatment with 4-iodoanisole (1.2 equiv), K_3PO_4 (1 equiv),

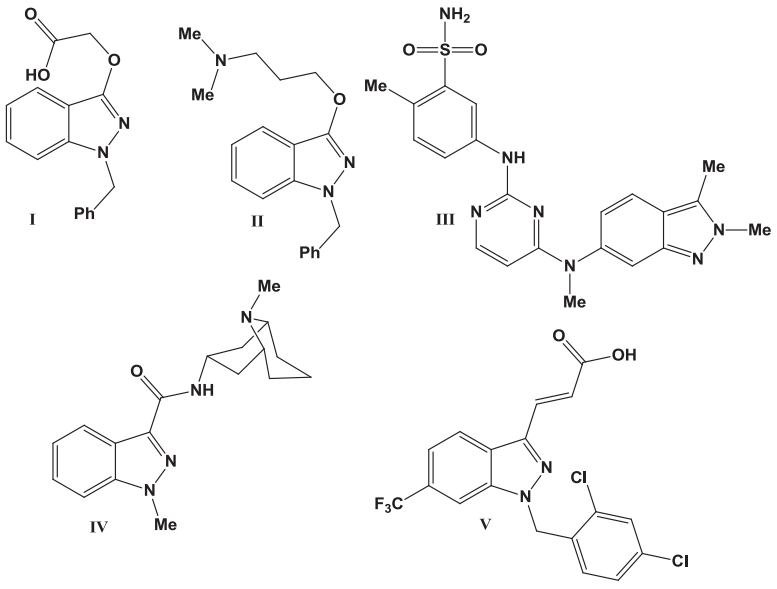


Fig. 1. Chemical structures of some drugs containing indazole.