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Reactivity of 5-aminopyrazoles bearing a cyclopropyl group at C3-position in palladium-catalyzed direct C4-arylation

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Abstract— Pyrazole derivatives bearing a cyclopropyl group at C3-position and an amino substituent at C5 were successfully employed in palladium-catalyzed direct arylations. These couplings were performed using air-stable PdCl(C₃H₅)(dppb) catalyst associated to KOAc as inexpensive base, and afforded regioselectively the C4-arylated pyrazoles without decomposition of the cyclopropyl unit and formation of amination products. A wide variety of functional groups on the aryl bromide including electron-withdrawing and electron-donating ones such as nitrile, nitro, propionyl, ester, trifluoromethyl, chloro, fluoro or methoxy was tolerated. Moreover, from 5-aminopyrazoles bearing *N*-2'-bromoaryl or 2'-bromobenzenesulfonamide substituent on the amino group, intramolecular Pd-catalyzed direct arylations allowed the formation of tricyclic compounds by formation of 5- or 6-membered rings. © 2018 Elsevier Science. All rights reserved

Keywords: palladium, C-H bond functionalization, pyrazoles, cyclopropyl, aryl bromides

1. Introduction

Pyrazoles derivatives bearing a cyclopropyl unit are of considerable interest for pharmaceutical chemists due to their biological activities. Several molecules containing a cyclopropylpyrazole moiety such as compounds **I-IV** exhibit properties against some cancers; and some of them such as **III** and **IV** are under *in vivo* and *in vitro* investigation in the field of insulin-like growth factor and IGF-1 receptor which play an important role in cancer [1,2]. Therefore, the development of simple and reliable methods for the synthesis of 3-cyclopropylpyrazol derivatives, especially using commercially available 3-cyclopropylpyrazoles is highly desirable.

Figure 1. Examples of bioactive cyclopropyl-substituted aminopyrazole derivatives.

The Pd-catalyzed direct arylation of a wide range of heteroaromatics [3-10], including pyrazoles [11-14], *via* a C–H bond activation of the heteroaromatics using aryl halides as aryl source has led to successes in recent years. Compared to classical palladium-catalyzed reactions such as Stille, Suzuki or Negishi couplings [15], such reactions are very attractive, as no preliminary preparation of organometallic derivatives is required. However, to our knowledge, no examples of palladium catalyzed direct arylations of pyrazoles bearing a cyclopropyl group has been described; whereas, several examples of preparation of C4-arylated 3-cyclopropylpyrazoles *via* Suzuki couplings have been reported in 2015-2017 (Scheme 1, top) [16-20]. On the other hand, several examples of Pd-catalyzed direct functionalizations of the very reactive sp^3 C–H bonds of cyclopropane units have been described [21-28]. Therefore, the tolerance to such cyclopropyl substituents on pyrazole in Pd-catalyzed direct arylations for a simple access to a variety of cyclopropyl-substituted pyrazole derivatives needed to be studied.

Herein, we report 1) on the influence of the nature of the base for the reaction of 3-cyclopropyl-1-methylpyrazol-5-amines with aryl bromides; 2) on the access to a wide variety of 4-arylated 3-cyclopropyl-1-methylpyrazol-5-amines using substituted aryl bromides; 3) on the formation of 5- and 6-membered rings through Pd-catalyzed intramolecular direct arylations of 5-aminopyrazoles bearing 2-bromoaryl substituents on the amino group (Scheme 1, bottom).

Previous work [16-20]

This work

Scheme 1. Access to C4-arylated 3-cyclopropyl-1-methylpyrazole derivatives *via* Pd-catalyzed reactions.

2. Results and discussion

First, we examined the influence of the reaction conditions for the coupling of 3-cyclopropyl-1-methylpyrazol-5-amine with 4-bromobenzonitrile (Table 1). Starting from a slight excess of the aryl bromide (1.5 eq.) with respect to the pyrazole derivative, in the presence of 2 mol% Pd(OAc)_2 as the catalyst, KOAc as the base, in DMA at 150°C , the desired product **1a** was obtained in only 51% yield (Table 1, entry 1). This moderate yield was due to a partial conversion of the pyrazole derivative; whereas no degradation of the cyclopropyl substituent was observed. It should be mentioned that, under these conditions, the amination product **1b** was not detected. The use of 2 mol% $\text{PdCl(C}_3\text{H}_5\text{)}(\text{dppb})$ catalyst [29] instead of

$\text{Pd}(\text{OAc})_2$ under the same conditions produces **1a** in 58-62% yields with complete conversion of the pyrazole derivative (Table 1, entry 2). The influence of a few bases on the selectivity and yield of the reaction was then examined, and both CsOAc and NaOAc led to mixtures of products **1a** and **1b** (Table 1, entries 3 and 4). On the other hand, no formation of **1a** was observed in the presence of Cs_2CO_3 as base, and the amination product **1b** was selectively obtained in 50% yield (Table 1, entry 6). The use of DMF as solvent with Cs_2CO_3 base allowed to slightly increase the yield in **1b** to 53% (Table 1, entry 7). The difference in selectivity observed depending on the nature of the base can be explained by the concerted metalation deprotonation (CMD) mechanism involved in the direct arylation. The good performance of acetates as base/palladium ligand in (CMD) pathway has been demonstrated by Fagnou [30].

Table 1. Influence of the reaction conditions for palladium-catalyzed arylation of 3-cyclopropyl-1-methylpyrazol-5-amine with 4-bromobenzonitrile.

Entry	Catalyst	Solvent	Base	Conv. (%)	Ratio 1a:1b	Yield in 1a (%)
1	$\text{Pd}(\text{OAc})_2$	DMA	KOAc	67	100:0	51
2	$\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$	DMA	KOAc	100	100:0	62, 58 ^b
3	$\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$	DMA	CsOAc	100	84:16	50
4	$\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$	DMA	NaOAc	38	80:20	nd
5	$\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$	DMA	K_2CO_3	100	10:90	nd
6	$\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$	DMA	Cs_2CO_3	100	0:100	50 ^a
7	$\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$	DMF	Cs_2CO_3	100	0:100	53 ^a

Conditions: $[\text{Pd}]$ (0.02 mmol), 4-bromobenzonitrile (1.5 mmol), 3-cyclopropyl-1-methylpyrazol-5-amine (1 mmol), base (2 mmol), 150 °C, 15 h, argon, conversion of 3-cyclopropyl-1-methylpyrazol-5-amine. ^a Yield in **1b**. ^b $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$ (0.1 mmol), 4-bromobenzonitrile (7.5 mmol), 3-cyclopropyl-1-methylpyrazol-5-amine (5 mmol), KOAc (10 mmol).

Then, the scope of the C4-arylation of 3-cyclopropyl-1-methylpyrazol-5-amine using 2 mol% $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$ catalyst, KOAc as the base and DMA as the solvent at 150 °C was examined (Scheme 2). First, the reactivity of a set of *para*-

substituted aryl bromides was studied. Good yields in the target products **2-6** were obtained from the electron-deficient aryl bromides bearing propionyl, ester, trifluoromethyl, chloro or fluoro substituents. Conversely, the use of 4-bromonitrobenzene afforded **7** in low yield due to the formation of several degradation products. From the electron-rich bromobenzenes bearing *tert*-butyl- or methoxy-substituents at *para*-position, the coupling products **8** and **9** were isolated in 75% and 51% yields, respectively. Then, three *meta*-substituted aryl bromides have been employed, and again, the use of 2 mol% PdCl(C₃H₅)(dppb) efficiently promoted the formation of **10-12** in 74-88% yields from bromobenzenes bearing nitrile, chloro, or trifluoromethyl substituents. Then, we employed a range of *ortho*-substituted aryl bromides. Lower yields were obtained with 2-bromobenzonitrile, 2-bromochlorobenzene than with the *para*-substituted aryl bromides. From these two reactants, the desired products **13** and **14** were obtained in 64% and 61% yields, respectively. Heteroaryl bromide 3-bromoquinoline was also a suitable coupling partner, as the product **17** was obtained in 91% yield.

Scheme 2. Palladium-catalyzed direct C4-arylation of 3-cyclopropyl-1-methylpyrazol-5-amine with (hetero)aryl bromides.

As our amination procedure employs a quite cheap base and simple conditions, we also studied the scope of this reaction in order to prepare *N*-arylated 3-cyclopropylpyrazoles (Scheme 3). A set of substituted aryl bromides has been reacted with 3-cyclopropyl-1-methylpyrazol-5-amine using 2 mol% PdCl(C₃H₅)(dppb) catalyst associated to Cs₂CO₃ as the base. These reaction conditions exclusively promoted the formation of the amination products **17-20** in 53-66% yields from bromobenzenes bearing nitrile, ester or even chloro substituents. Moreover, from 1,2-dibromobenzene, product **21** was obtained in 63% yield, without cleavage of the second C-Br bond, allowing further transformations.

Scheme 3. Palladium-catalyzed amination of 3-cyclopropyl-1-methylpyrazol-5-amine with aryl bromides.

Then, we examined the reactivity of the previously obtained *N*-arylated pyrazoles **1b** and **21** (see table 1, entry 7 and scheme 3) using direct arylation reaction conditions (Scheme 4). From 4-bromochlorobenzene and **1b**, the C4-arylation product **22** was obtained in 76% yield (Scheme 4, top). Even the bromo-substituted *N*-arylpyrazole **21** was successfully arylated at C4-position using 4-bromobenzonitrile as aryl source, affording product **23** in 71% yield, without cleavage of the C-Br bond of the aryl on the pyrazolyl derivative (Scheme 4, bottom). No Pd-catalyzed intramolecular cyclization of **21** to give **24** (see scheme 5) was detected. This selectivity is due to the easier oxidative addition of 4-bromobenzonitrile compared to the 2-bromoaniline unit to palladium.

Scheme 4. Palladium-catalyzed direct C4-arylation of 3-cyclopropyl-1-methylpyrazol-5-amine derivatives with aryl bromides.

The synthesis of 1,8-dihydropyrazolo[3,4-*b*]indoles bearing a cyclopropyl unit at C3-position has not been reported so far. Therefore, we investigated the reactivity of compound **21** in Pd-catalyzed intramolecular direct arylation (Scheme 5, top).

The use of 2 mol% $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$ catalyst in the presence of KOAc at 150 °C gave selectively the desired 3-cyclopropylpyrazolo[3,4-*b*]indole derivative **24** in 88% yield. No intermolecular coupling was detected in the course of this reaction.

To our knowledge, the synthesis of 3,4-dihydrobenzo[*e*]pyrazolo[3,4-*c*][1,2]thiazines has never been described. In order to have access to a 3,4-dihydrobenzo[*e*]pyrazolo[3,4-*c*][1,2]thiazine, we prepared the 2-bromo-*N*-(pyrazol-5-yl)benzenesulfonamide derivative **25** by reaction of 3-cyclopropyl-1-methylpyrazol-5-amine with 2-bromobenzenesulfonyl chloride (Scheme 5, bottom). Using product **25** and 2 mol% $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$ catalyst associated to KOAc at 150 °C, no trace of the desired cyclization product **27** was detected. Conversely, the sulfonamide **26** bearing both a pyrazolyl and a propyl group on the nitrogen atom, under the same reaction conditions, afforded the target tricyclic product **28** in very high yield.

Scheme 5. Formation of 5- and 6-membered rings *via* palladium-catalyzed intramolecular direct arylations.

In summary, we have demonstrated that using $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$ catalyst in the presence of KOAc base, the C4-arylation *via* C-H bond activation of 3-cyclopropyl-1-methylpyrazol-5-amine proceeds in moderate to high yields. Conversely, the use of Cs_2CO_3 base afforded the amination product. No decomposition of the cyclopropyl group was observed for both procedures.

The direct arylation procedure gave good results using both electron-rich and electron-deficient aryl bromides. Several useful functional groups such as propionyl, ester, nitro, nitrile, trifluoromethyl, chloro, fluoro or methoxy were tolerated on the aryl bromide, and even the heteroarene 3-bromoquinoline gave a satisfactory result. Moreover, from 5-aminopyrazoles bearing *N*-2'-bromoaryl or 2'-bromobenzenesulfonamide substituents on the amino group, intramolecular Pd-catalyzed direct arylations allowed the formation of 5- or 6-membered rings. This procedure is attractive from both synthetic and environmental points of view, as with this C-H bond functionalization procedure, no preparation of an organometallic derivative is required, and as the major waste of this coupling reaction is the relatively non-toxic AcOH/KBr instead of the mixture of metallic salts obtained with more classical metal-catalyzed coupling reactions. For these reasons, this methodology is very promising for the tuning of the biological properties of cyclopropyl-substituted pyrazoles.

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*Highlights (for review)

- Selective arylation of 3-cyclopropyl-1-methylpyrazol-5-amine at C4 position
- amination *vs* arylation is controlled by the nature of base and solvent
- Intramolecular reactions allow the synthesis of polycyclic aromatics

Intramolecular C-H Bond Arylation

Graphics Abstract

Figure 1