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Palladium-catalyzed selective C5—H bond arylation of pyrazole using hydroxymethyl substituent as blocking group

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ABSTRACT

In this study, we investigated the reactivity of two unprotected hydroxymethyl-substituted pyrazoles in palladium-catalyzed C—H arylation. The conditions for the regioselective C5-arylation of (1-methylpyrazol-4-yl) methanol, while leaving the hydroxymethyl function intact, have been established. The reaction demonstrates broad substrate compatibility, accommodating a diverse array of electron-deficient and electron-excessive aryl bromides, including those bearing substituents in the *para*-, *meta*- and *ortho*-positions and is compatible with heteroaryl bromides. Furthermore, the reaction uses only 2 mol% of an air-stable palladium catalyst and KOPiv as an inexpensive base. This method enables the synthesis of a diverse range of pyrazole derivatives in a single step, thus facilitating the straightforward modification of their biological properties.

Introduction

It is noteworthy that a significant number of pharmaceutical compounds incorporate an arylpyrazole moiety [1]. For example, 5-arylpyrazoles include both Celecoxib, a nonsteroidal anti-inflammatory drug, and Nidufexor, an experimental treatment for nonalcoholic steatohepatitis (Fig. 1, top). Crizotinib, a 4-arylpyrazole, is an anti-cancer drug approved in 2011 for the treatment of certain non-small cell lung carcinomas, and Zanubrutinib, a 3-arylpyrazole, is another anti-cancer drug that received approval in 2019 for the treatment of specific lymphomas (Fig. 1, bottom). Although numerous approaches to the synthesis of substituted pyrazoles have been described [2], the development of simple and straightforward methodologies for the synthesis of arylpyrazoles bearing useful functional groups is still needed.

An important research topic in organic chemistry is the palladium-catalyzed direct C—H bond functionalization of (hetero)arenes [3]. Over the past few decades, a number of methods have been reported for the control of such C—H bond functionalization. The palladium-catalyzed C—H arylation of five-membered ring heteroarenes is becoming an increasingly reliable approach for the one-step synthesis of arylated heteroarenes, offering a promising alternative to existing methods [3,4]. Indeed, in comparison with Stille, Suzuki or Negishi coupling reactions, this method is particularly advantageous, as it circumvents the necessity for the prior synthesis of organometallic

derivatives. In the case of most five-membered ring heteroarenes, such as furans, (benzo)thiophenes or pyrroles, the positions that demonstrate the highest reactivity are C2 and C5 [5]. Another notable advantage of this coupling reaction is its remarkable versatility in accommodating a wide range of useful reactive functional groups, including unprotected alcohols [6]. However, this approach has a significant limitation, namely the control of the regioselectivity of this type of coupling, since for some substrates, more than one C—H bond of the heteroarenes may undergo arylation, resulting in the formation of mixtures of isomers [5]. For example, the Pd-catalyzed C—H arylation of 1-SEM-pyrazole (SEM = 2-(trimethylsilyl)ethoxymethyl), which was reported by Sames et al. resulted in the formation of 5-phenylpyrazole, 4-phenylpyrazole and 4,5-diphenylpyrazole in 4:1:3 ratio [7]. The results of this study demonstrate that the 5-position exhibits a higher degree of reactivity in comparison to the 4-position, while the 3-position displays a markedly lower level of reactivity [7]. Consequently, with many pyrazoles, mixtures of arylation products were obtained [8]. In order to control the regioselectivity of the pyrazoles arylation, several research groups have employed a variety of blocking groups at the pyrazole C4 position. These include formyl [9,10], ester [9], chloro [11], bromo [11], nitrile [9] and nitro [12] substituents (Scheme 1, top). The use of such blocking groups enabled the selective synthesis of C5-arylated pyrazoles via a palladium-catalyzed C—H activation in high yields. To the best of our knowledge, the use of hydroxymethyl as a blocking group on pyrazoles in palladium-

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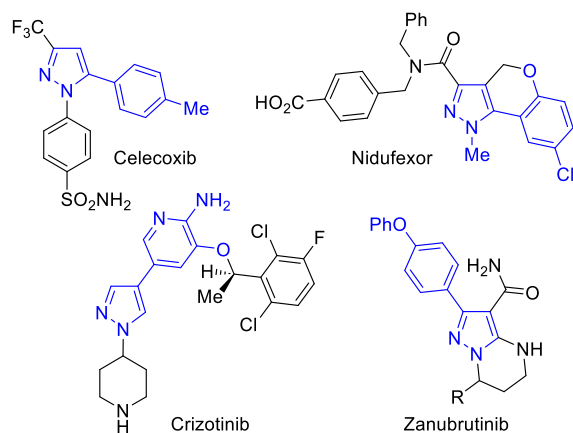
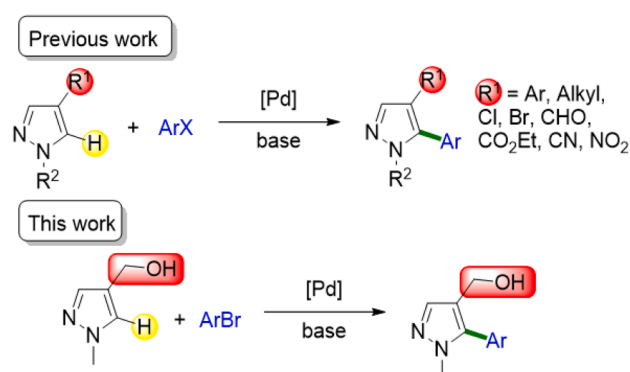


Fig. 1. Selected drugs containing an arylpyrazole unit.



- Hydroxymethyl: A new blocking group at pyrazole C4-position
- No need to protect hydroxymethyl function
- Regioselective direct arylation at C5-position
- Pyrazole hydroxymethyl substituent can be utilized in a variety of organic reactions

Scheme 1. Pd-catalyzed direct arylation of 4-substituted pyrazoles.

catalyzed direct arylation has not been reported. In order to further extend the substrate scope of the Pd-catalyzed direct arylation of substituted pyrazoles, we investigated the reactivity of unprotected C4- and C5-methanol substituted pyrazoles (Scheme 1, bottom). The presence of the hydroxymethyl functional group on building blocks in organic synthesis is very attractive because of its enormous versatility in a variety of organic transformations. This report describes *i*) conditions for the Pd-catalyzed regioselective C–H C5-arylation of unprotected (1-methylpyrazol-4-yl)methanol; *ii*) the spectrum of aryl bromides in this process; *iii*) on the reactivity of (1-methylpyrazol-5-yl)methanol in Pd-catalyzed C–H bond arylation.

Results and discussion

Firstly, the outcome of the reaction between a mixture of (1-methylpyrazol-4-yl)methanol (1.5 equiv.) and 1-bromo-4-chlorobenzene (1 equiv.) in the presence of 2 mol% PdCl(C₃H₅)(dppb) catalyst [13], KOAc base and DMA as the solvent at 140 °C was established (Table 1). These reaction conditions had been previously identified as effective in promoting the Pd-catalyzed C–H bond arylation of several 5-membered ring heteroarenes [8a]. Under these conditions, the C5-arylated pyrazole **1** was obtained in 48 % yield, accompanied by the formation of a notable quantity of the 4,4'-dichloro-1,1'-biphenyl by-product (Table 1, entry 1). In the course of this reaction, no C3-arylation or arylation of the hydroxymethyl unit of the pyrazole ring was observed. The influence of several bases was investigated. CsOAc was found to be ineffective,

Table 1

Influence of the reaction conditions on the Pd-catalyzed arylation of (1-methylpyrazol-4-yl)methanol with 1-bromo-4-chlorobenzene.

Entry	Catalyst	Solvent	Base	Temp. (°C)	Conv. (%)	Yield in 1 (%)
1	PdCl (C ₃ H ₅)(dppb)	DMA	KOAc	140	89	48
2	PdCl (C ₃ H ₅)(dppb)	DMA	CsOAc	140	100	0
3	PdCl (C ₃ H ₅)(dppb)	DMA	NaOAc	140	94	12
4	PdCl (C ₃ H ₅)(dppb)	DMA	K ₂ CO ₃	140	90	0
5	PdCl (C ₃ H ₅)(dppb)	DMA	Cs ₂ CO ₃	140	83	<5
6	PdCl (C ₃ H ₅)(dppb)	DMA	KOPiv	140	100	66, 62 ^a
7	PdCl (C ₃ H ₅)(dppb)	DMA	KOPiv	130	88	56
8	PdCl (C ₃ H ₅)(dppb)	DMF	KOPiv	140	100	31
9	PdCl (C ₃ H ₅)(dppb)	NMP	KOPiv	140	100	17
10	PdCl (C ₃ H ₅)(dppb)	xylene	KOPiv	140	100	<5
11	PdCl (C ₃ H ₅)(dppb)	3-methylbutan-1-ol	KOPiv	140	73	23
12	PdCl (C ₃ H ₅)(dppb)	DMA/3-methylbutan-1-ol 8:1	KOPiv	140	100	60
13	Pd(OAc) ₂	DMA	KOPiv	140	94	33

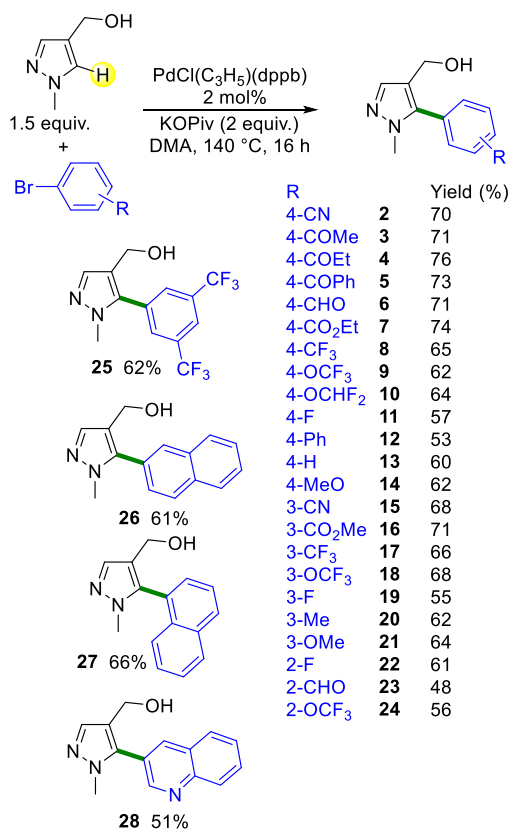
Conditions: [Pd] (0.02 mmol), 1-bromo-4-chlorobenzene (1 mmol), (1-methylpyrazol-4-yl)methanol (1.5 mmol), base (2 mmol), 16 h, conversion of 1-bromo-4-chlorobenzene, isolated yields.

^a PdCl(C₃H₅)(dppb) (0.1 mmol), 1-bromo-4-chlorobenzene (5 mmol), (1-methylpyrazol-4-yl)methanol (7.5 mmol), KOPiv (10 mmol).

whereas NaOAc led to the generation of **1** in 12 % yield (Table 1, entries 2 and 3). The use of carbonate bases, namely K₂CO₃ and Cs₂CO₃, also proved ineffective (Table 1, entries 4 and 5). Although it is known that the formation of ethers from aryl bromides and hydroxymethyl-substituted arenes can be achieved using palladium catalysts and Cs₂CO₃ as a base, the resulting ether was also not detected under these conditions [14]. Conversely, a high yield of 66 % in target product **1** was obtained with KOPiv as the base (Table 1, entry 6). Moreover, when the same procedure was carried out on a gram scale, the yield in **1** was found to be 62 %, indicating that the reaction proceeded in a similar manner. These results are consistent with the concerted metalation–deprotonation (CMD) mechanism, which involves the coordination of the base to the palladium complex in order to activate the C–H bond. It has been demonstrated that acetates and pivalates constitute the most efficacious bases in this CMD process [15,16]. A reduction in the reaction temperature from 140 °C to 130 °C resulted in a decrease in the yield of product **1**, due to the partial conversion of the starting material,

1-bromo-4-chlorobenzene (Table 1, entry 7). Subsequently, the impact of various solvents was evaluated. DMF and NMP resulted in lower yields in **1** compared to DMA, whereas xylene proved to be ineffective (Table 1, entries 8–10). The use of the environmentally-friendly solvent 3-methylbutan-1-ol resulted in a low yield of 23 % for product **1** (Table 1, entry 11). The combination of DMA and 3-methylbutan-1-ol proved effective in yielding product **1** with a higher yield of 60 % (Table 1, entry 12). This indicates that a mixture of such solvents can be used, allowing to reduce the amount of the rather toxic solvent DMA for such couplings. Finally, the use of a phosphine-free catalyst, namely Pd(OAc)₂, afforded the desired product **1** in 33 % yield (Table 1, entry 13).

Subsequently, a diverse array of *ortho*-, *meta*-, and *para*-substituted aryl bromides was reacted with (1-methylpyrazol-4-yl)methanol, utilizing PdCl(C₃H₅)(dppb) catalyst (2 mol%), along with KOPiv as the base in DMA at 140 °C (Scheme 2) [17,18]. The synthesis of C5-arylated pyrazoles **2–9** was accomplished by employing electron-deficient aryl bromides *para*-substituted with nitrile, acetyl, propionyl, benzoyl, formyl, ester, trifluoromethyl, or trifluoromethoxy groups. The reaction proceeded with complete selectivity and afforded the target compounds in 62–76 % yields. It is noteworthy that the presence of acetyl or formyl substituents — which have been shown to be sensitive to the presence of bases or Pd-catalysts — on the *para*-position of aryl bromides, did not result in any deleterious effects on the reaction outcome. The use of a difluoromethoxy *para*-substituent resulted in the formation of product **10**, with a yield comparable to that observed in the previous experiments. The presence of fluoro and phenyl substituents in the *para*-position of the aryl bromide, which exert no significant electronic influence, and bromobenzene, resulted in products yields between 53 and 60 % for compounds **11–13**. It is noteworthy that the electron-rich 4-bromoanisole, which has been observed to exhibit reduced reactivity for some palladium-catalyzed reactions, gave product **14** with a yield of 62 %. The C5-arylated pyrazoles **15–18** were also obtained in good



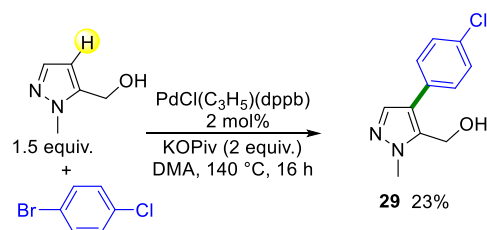
Scheme 2. Scope of the Pd-catalyzed direct C5-arylation of (1-methylpyrazol-4-yl)methanol.

yields (66–71 %) from the nitrile, ester, trifluoromethyl, and trifluoromethoxy *meta*-substituted aryl bromides. Similarly, target products **19** and **20** were obtained with similar yields from 3-fluorobromobenzene and 3-bromotoluene. Furthermore, target product **21** was produced in a satisfactory yield when less activated 3-bromoanisole was employed as the starting material. We also explored the reactivity of three *ortho*-substituted aryl bromides. The reactions involving 2-fluorobromobenzene, 2-bromobenzaldehyde and 2-(trifluoromethoxy)bromobenzene were successful, resulting in the production of the compounds **22–24** in yields ranging from 48 % to 56 %. The relatively low yield of 48 % observed in the reaction involving 2-bromobenzaldehyde can be attributed to the formation of unidentified byproducts. A higher yield of 62 % of the desired C5-arylated pyrazole **25** was achieved by utilizing the disubstituted 1,3-bis(trifluoromethyl)-5-bromobenzene as the precursor. Additionally, both 2-bromonaphthalenes and 1-bromonaphthalenes can be employed in this reaction, resulting in the formation of the products **26** and **27** in yields of 61 % and 66 %, respectively. The *N*-containing heteroaromatic 3-bromoquinoline also furnished the desired arylated pyrazole **28** in a 51 % yield. The difference between theoretical yields, which should be 100 %, and isolated yields is due to the formation of some degradation products and the formation of small amounts of 1-methyl-5-arylpyrazole-4-carbaldehyde derivatives as by-products. This method compares favorably to those using ester [9], or nitrile [9] blocking groups, as the substrate range using these two groups was very limited. In comparison to the reactions utilizing bromo [11] or chloro [11] blocking groups, this methodology provides a more straightforward approach to the formation of diverse pyrazole derivatives through the use of the hydroxymethyl functional group.

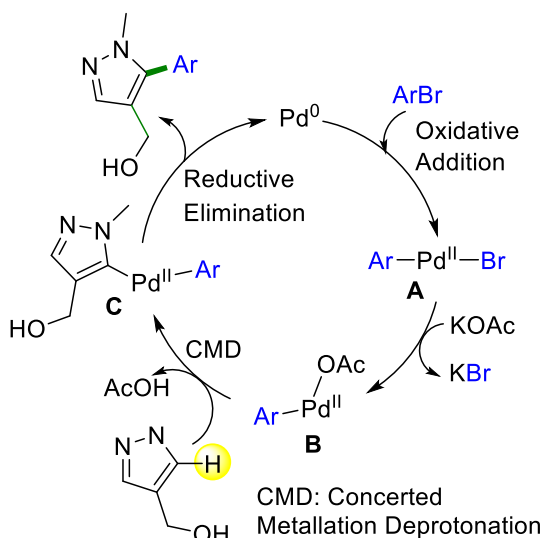
The reactivity of (1-methylpyrazol-5-yl)methanol for C4 arylation was also investigated (Scheme 3). Under the same reaction conditions as those used for the arylation of (1-methylpyrazol-4-yl)methanol using 1-bromo-4-chlorobenzene as reaction partner, only 23 % of the target product **29** was obtained due to low starting material conversion. Using 4-bromobenzonitrile and 4-bromoacetophenone as reaction partners gave even more disappointing results, as the desired coupling products could not be isolated.

Mechanism for the C5-arylation of (1-methylpyrazol-4-yl)methanol, certainly proceed via a classical direct arylation mechanism as described in the Scheme 4. The first step of the catalytic cycle involves the oxidative addition of the aryl bromide to palladium to give the intermediate ArPdBr **A**. The intermediate ArPdOAc **B** is obtained by ligand exchange. Then, after a concerted metallation deprotonation (CMD) [16] of the pyrazole coupling partner, the intermediate **C** is obtained. Finally, a reductive elimination provides the C5-arylated pyrazoles with regeneration of the Pd(0) catalyst.

In conclusion, the results demonstrate that hydroxymethyl is an effective blocking group at the pyrazole C4-position, allowing for regioselective direct arylation at C5-position. The versatility of hydroxymethyl substituents as reagents in a multitude of organic reactions has been established, rendering the use of such blocking groups an attractive approach in organic synthesis. When the coupling reaction was carried out under suitable conditions, the hydroxymethyl function was not affected and regioselective arylation was observed at the C5



Scheme 3. Direct Pd-catalyzed C4-arylation of (1-methylpyrazol-5-yl)methanol.



position of the pyrazole, whereas no arylation was detected at the C3 position. The reaction tolerates a very wide range of functional groups on the aryl bromides in the *para*-, *meta*- and even *ortho*-positions. In addition, the absence of protection and deprotection steps on the hydroxymethyl functional group and the use of only 2 mol% of an air-stable palladium catalyst and KOPiv as an inexpensive base makes this one-step process very attractive for accessing (5-arylpiperazine-4-yl) methanol derivatives.

CRedit authorship contribution statement

Rabeb Ben Romdhane: Methodology, Investigation, Formal analysis. **Ridha Ben Salem:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Henri Doucet:** Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data (experimental procedures, product characterization and copies of the ^1H and ^{13}C NMR for all compounds) to this article can be found online at <https://doi.org/10.1016/j.tetlet.2025.155465>.

Data availability

Data will be made available on request.

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(c) D. Lapointe, K. Fagnou, *Chem. Lett.* **39** (2010) 1118–1126.
- [17] General procedure for the synthesis of C5-arylated (1-methylpyrazol-4-yl)methanol derivatives (Scheme 2): To a 25 mL oven dried Schlenk tube, aryl bromide (1 mmol), (1-methylpyrazol-4-yl)methanol (0.168 g, 1.5 mmol), KOPiv (0.280 g, 2 mmol) in the presence of PdCl(C₃H₅)(dppb) (12.1 mg, 0.02 mmol) and DMA (4 mL) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 140 °C (oil bath temperature) for 16 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the C5-arylated (1-methylpyrazol-4-yl)methanol derivatives.
- [18] Synthesis of (5-(4-chlorophenyl)-1-methylpyrazol-4-yl)methanol (1): From 1-bromo-4-chlorobenzene (0.192 g, 1 mmol) and (1-methylpyrazol-4-yl)methanol (0.168 g, 1.5 mmol), product 1 was obtained in 66% yield (0.147 g) as a white solid: mp 127–129 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.60 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 4.46 (s, 2H), 3.81 (s, 3H), 1.75 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 140.9, 138.8, 135.1, 131.0, 129.1, 127.8, 119.7, 55.5, 37.3. HRMS calcd for [M+Na]⁺ C₁₁H₁₁ClN₂O₂Na 245.0452, found 245.0454.