第 26 卷 第 3 期 催 化 学 报 2005 年 3 月
Vol. 26 No. 3 *Chinese Journal of Catalysis* March 2005

Article ID：0253-9837(2005)03-0173-02 **Communication**：173～174

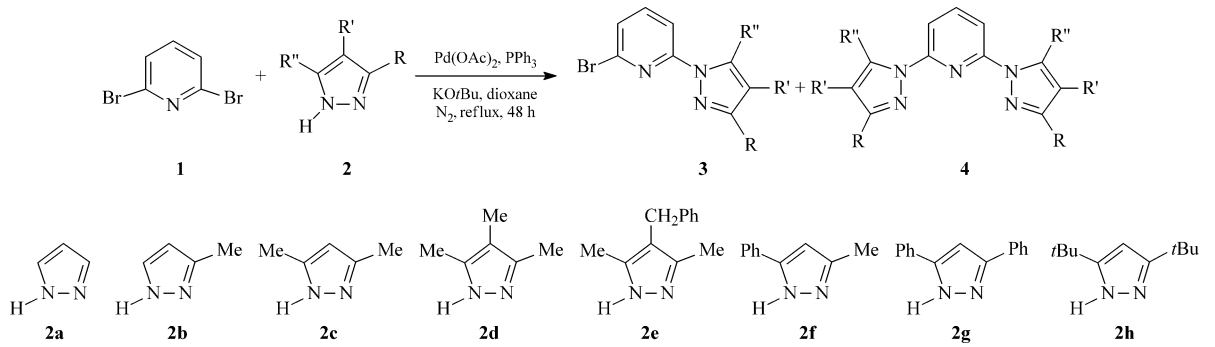
Palladium-Catalyzed Coupling of Pyrazoles with 2,6-Dibromopyridine

SUN Xiaojiao[1], YU Zhengkun[1], DENG Haixia[2], WU Xiaowei[1], WU Sizhong[1], DONG Jinhua[2]
(*1 Dalian Institute of Chemical Physics, The Chinese Academy of Sciences, Dalian 116023, Liaoning, China*;
2 School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang 110016, Liaoning, China)

Key words：palladium, pyrazole, 2,6-dibromopyridine, coupling, potassium *tert*-butoxide
CLC number：O643 **Document code**：A

A rich chemistry involving pyrazoles[1] and pyrazolato ligands[2] has evolved since pyrazoles were first prepared in 1968[3], due to the potential bioactivity of pyrazole derivatives and their use as ligands. Phosphorus-based ligands play a very important role in organic synthesis and catalysis. Recently, new classes of ligands with donor atoms other than phosphorus, particularly nitrogen donor ligands, have been paid more and more attention because phosphine ligands easily undergo degradation, and organometallic complexes bearing nitrogen donor ligands show high activity. 2,6-Bis(*N*-pyrazolyl)pyridines (**4**) were first prepared from the reactions of 2,6-dihalopyridines and potassium pyrazolates under harsh conditions[4], and have been paid little attention[5]. The CuI-catalyzed *N*-arylation of 3-bromopyridine and aromatic halides with **2a**～**2c** or other less bulky pyrazoles was reported in Ref [6].

In order to synthesize **4**, the coupling reactions of 2,6-dibromopyridine (**1**) and pyrazoles (**2**) catalyzed by $Pd(OAc)_2$ in the presence of a base were studied under the mild conditions, and the preliminary results are reported here, the synthesis route used is shown in Scheme 1.



Scheme 1 Synthesis of 2,6-bis(*N*-pyrazolyl)pyridines

Pyrazoles **2a**～**2h** were used, and the steric hindrance of the substituents on the corresponding pyrazolato ring follows the order：**2a**＜**2b**＜**2c**＜**2d**＜**2e**＜**2f**＜**2g**＜**2h**. Using $Pd(OAc)_2$ as the catalyst and PPh_3 as the ligand, **1** reacted with **2** in the presence of the base, potassium *tert*-butoxide, in dioxane at the refluxing temperature of 102 ℃ for 48 h. Compounds **3** and/or **4** were collected by silica gel column chromatography.

Table 1 shows the coupling result of **1** and **2** in the molar ratio of 1∶2.4. Surprisingly, **4** was the minor product in the presence of the catalyst except that **2a** was used, but it was the major product in the most cases without catalyst. In the case of **2a**, **4** was the major product with the yield of 69.2%. In other cases, **3** was the major product. It is noteworthy that the most steric pyrazole **2h** did not react with **1** to form **3** nor **4**, and the second most steric pyrazole **2g**

Received date：2004-12-25. **First author**：SUN Xiaojiao, female, born in 1981, MS student.
Corresponding author：YU Zhengkun. Tel：(0411)84379227；E-mail：zkyu@dicp.ac.cn.
Foundation item：Supported by the "Hundred-Talented" Program Funding of The Chinese Academy of Sciences.

Table 1 Coupling of compounds 1 and 2 in the molar ratio of 1∶2.4

Pyrazole	With catalyst[a]		Without catalyst	
	Y(3)/%	Y(4)/%	Y(3)/%	Y(4)/%
2a	28.9[b]	69.2[b]	45.5	54.5
2b	64.0[c]	35.2[c]	36.1[c]	62.5[c]
2c	57.4[b]	34.7[b]	36.8	54.1
2d	58.3[b]	30.3[b]	40.2	59.2
2e	66.3	25.0	42.7	54.8
2f	64.9	29.6	58.3	41.6
2g	28.6	0	32.9	0
2h	0	0	0	0

[a] 10mol% $Pd(OAc)_2$ and 20mol% PPh_3 were used unless stated otherwise.

[b] 5mol% $Pd(OAc)_2$ and 10mol% PPh_3 were used.

[c] Two regioisomers were detected by ^1H NMR.

The yield was calculated on the basis of compound **1**.

Reaction conditions: $n(\mathbf{1}) = 2.0$ mmol, $n(\mathbf{2}) = 4.8$ mmol, $n(KO\mathit{t}Bu) = 5.0$ mmol, $V(\text{dioxane}) = 10$ ml, $\theta = 102$ ℃, $t = 48$ h, the same below unless stated otherwise.

only gave the mono-substituted product **3** with low yield. Without the presence of $Pd(OAc)_2/PPh_3$, **4** was the major product except in the cases of **2f**～**2g**.

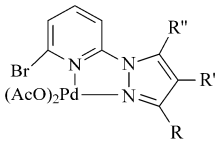
The coupling of **1** and **2** in the molar ratio of 1∶1 (shown in Table 2) selectively produced **3** with high yield and only a small or trace amount of **4** was detected in the reaction mixtures. During the reaction, both the coordination of the N−H of **2** and C−Br of **1** or **3** to the metal center led to the coupling of **1** and **2** to form **3**, and then **3** and **2** to form **4**, subsequently, the pyrazolate anions, which generated from the competitive deprotonation of the N−H of **2** by the potassium *tert*-butoxide, attacked **1** and/or **3**, to give **3** and/or **4**, respectively.

Table 2 Coupling of compounds 1 and 2 in the molar ratio of 1∶1

Pyrazole	With catalyst[a]		Without catalyst	
	Y(3)/%	Y(4)/%	Y(3)/%	Y(4)/%
2a	72.6[b]	2.1[b]	72.8	5.1
2b	76.0[c]	trace	66.3[c]	trace
2c	41.9[b]	trace	68.7	trace
2d	53.7[b]	trace	56.8	trace
2e	43.1	trace	59.3	trace
2f	76.0	trace	82.3	trace
2g	11.4	0	19.1	0
2h	0	0	0	0

Reaction conditions: $n(\mathbf{1}) = 2.0$ mmol, $n(\mathbf{2}) = 2.0$ mmol, $n(KO\mathit{t}Bu) = 2.0$ mmol.

The possible formation of **5** by the reaction of $Pd(OAc)_2$ and **3** as shown in Scheme 2 decreased the coordination of the N−H of **2** and C−Br of **3** to the metal, which increased the steric hindrance around the C−Br bond, and thus inhibited the catalytic activity of the $Pd(OAc)_2/PPh_3$ system.



Scheme 2 Structure of compound 5

References

1 Radi S, Ramdani A, Lekchiri Y, Morcellet M, Crini G, Janus L. *Tetrahedron*, 2004, **60**(4): 939

2 Sirimanne C T, Knox J E, Heeg M J, Schlegel H B, Winter C H. *J Am Chem Soc*, 2003, **125**(37): 11152

3 Elguero J, Gonzalez E, Jacquier R. *Bull Soc Chim Fr*, 1968, 707

4 Jameson D L, Goldsby K A. *J Org Chem*, 1990, **55**(17): 4992

5 Beach N J, Spivak G J. *Inorg Chim Acta*, 2003, **343**(): 244

6 Antilla J C, Baskin J M, Barder T E, Buchwald S L. *J Org Chem*, 2004, **69**(17): 5578

钯催化下吡唑与 2,6-二溴吡啶的偶联反应

孙小娇[1], 余正坤[1*], 邓海霞[2], 吴小伟[1], 吴思忠[1], 董金华[2]

(1 中国科学院大连化学物理研究所, 辽宁大连 116023; 2 沈阳药科大学制药工程学院, 辽宁沈阳 110016)

摘要: 在相对温和的反应条件以及 PPh_3 和 $KO\mathit{t}Bu$ 存在的情况下, $Pd(OAc)_2$ 催化吡唑与 2,6-二溴吡啶(摩尔比 1∶2.4)的偶联反应主要生成单吡唑基取代的 2-溴-6-吡唑基吡啶. 在无 $Pd(OAc)_2/PPh_3$ 存在的情况下, 则主要生成双吡唑基取代的 2,6-二吡唑基吡啶. $Pd(OAc)_2$ 与 2-溴-6-吡唑基吡啶反应生成的配合物中间体可能抑制了双吡唑基取代产物的生成, 从而影响产物分布.

关键词: 钯, 吡唑, 2,6-二溴吡啶, 偶联, 叔丁醇钾

(Ed YHM)