Tetrahedron Letters 54 (2013) 1401–1404

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Cu-mediated selective O-arylation on C-6 substituted pyridin-2-ones

Taijie Chen [a], Qingqing Huang [b], Yu Luo [a,*], Youhong Hu [c,*], Wei Lu [b]

[a] Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, China
[b] Institute of Drug Discovery and Development, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, China
[c] Shanghai Institute of Materia Medica, Chinese Academy of Science, 555 Zu Chong Zhi Road, Shanghai 201203, China

ARTICLE INFO

Article history:
Received 28 September 2012
Revised 20 December 2012
Accepted 28 December 2012
Available online 10 January 2013

Keywords:
Chan–Evans–Lam cross-coupling
Arylboronic acids
Selectivity
O-arylation
Pyridin-2-ones

ABSTRACT

A practical and mild strategy has been developed for the selective O-arylation on C-6 substituted pyridin-2-ones with a series of arylboronic acids, using $Cu(OTf)_2$ as the catalyst, DABCO as the ligand, Et_3N as the base, and K_2HPO_4 as the additive. This method affords O-arylated pyridin-2-ones with good selectivity and yields

Transition metal-mediated carbon–carbon and carbon–heteroatom coupling reactions are important tools in organic synthesis and have been widely used in the synthesis of natural products and pharmaceutical agents. Compared to palladium and other transition metals, copper salts are less toxic, less expensive, earth-abundant, and stable in air. Thus, copper-catalyzed cross-coupling has attracted many chemists' interest. The traditional Ullmann and Goldberg procedures played an important role in the synthesis of biaryl ethers. However, vigorous reaction conditions, such as high temperature, stoichiometric amounts of catalysts, and specific halide substrates, limited the use of this methodology. In 1998, Chan,[1] Evans,[2] and Lam[3] developed a new copper-catalyzed N/O-arylation methodology, using aryl boronic acids as the substrates. This method has been soon proven to be a powerful and attractive synthetic tool to construct carbon–heteroatom bond and widely used in the synthesis of many biologically active compounds.[4,5]

To date, many compounds with the 2-aryloxypyridine moiety have been reported to show various biological activities, such as herbicidal activity,[6] antispasmodic activity,[7] anti-bacterial activity,[8] M5 positive allosteric modulators activity,[9] anti-mycobacterial activity,[10] obesity-induced insulin resistance inhibitive activity, and anticancer activity.[11] Since 2-aryloxypyridine derivatives widely occur in biologically active molecules and chemical products, it is highly desired to develop a practical and efficient approach to diverse 2-aryloxypyridine derivatives.

Although several accounts of N-arylation of pyridin-2-ones with aryl halides[12,13] or arylboronic acids[14] have been reported, few literatures exist on the selective O-arylation of pyridin-2-ones.[15] Herein, we present a selective O-arylation method on C-6 substituted pyridin-2-ones, using Chan–Evans–Lam cross-coupling reaction.

To screen suitable reaction conditions, we focused on the coupling of 6-methyl pyridin-2-ones (**1**) and phenylboronic acid (**2**). As shown in Table 1, among the six copper catalysts screened, $Cu(OTf)_2$ gave a 30% yield of O-arylated compound **3**. Although the N/O selectivity was not satisfactory (41% yield of N-arylated compound **4** obtained), $Cu(OTf)_2$ was still the most effective catalyst. $Cu(NO_3)_2{\cdot}3H_2O$ (entry 4) could also produce the desired product **3**, nevertheless the yield was slightly lower than that of $Cu(OTf)_2$. Thus, $Cu(OTf)_2$ was determined as the appropriate catalyst and was used in the subsequent screening.

Secondly, different solvents were surveyed as shown in entries 7–11. It was found that both the yield and the selectivity of O-arylation were dramatically improved by using DMSO as the solvent (entry 8).

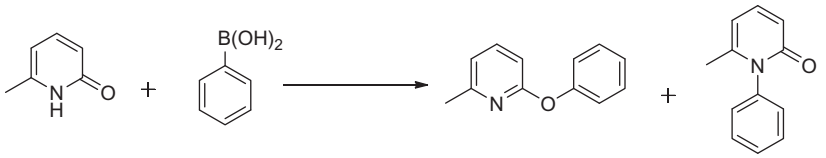
Subsequently, different ligands were investigated (entries 12–16). The most surprising results were obtained when DABCO was used as the ligand, which produces only O-arylated compound **3** without N-arylated product in 28% yield.

Recently, some literatures clarified[16,17] the significance of base and K_2HPO_4 in Cu(II)-mediated couplings. Bases, such as Et_3N could capture hydrogen proton and thus promote the formation of the

* Corresponding authors. Tel./fax: +86 21 6260 2475 (Y.L.); tel./fax: +86 21 5080 5896 (Y.H.).
E-mail addresses: yluo@chem.ecnu.edu.cn (Y. Luo), yhhu@mail.shcnc.ac.cn (Y. Hu).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.12.126

Table 1
Survey of copper salts with TMEDA[a]

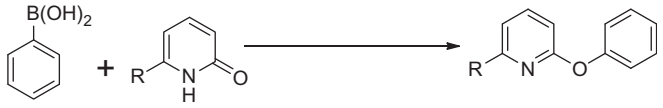


1 2 3 4

Entry	Copper source	Solvent	Ligand	Additive	**3**/Yield[b] (%)	**4**/Yield[b] (%)
1	$Cu(OTf)_2$	CH_2Cl_2	TMEDA	—	30	41
2[c]	$Cu(OAc)_2$	CH_2Cl_2	TMEDA	—	/	/
3[d]	$CuSO_4$	CH_2Cl_2	TMEDA	—	/	/
4	$Cu(NO_3)_2{\cdot}3H_2O$	CH_2Cl_2	TMEDA	—	20	10
5[c]	$CuCl_2$	CH_2Cl_2	TMEDA	—	/	/
6[c]	CuI	CH_2Cl_2	TMEDA	—	/	/
7[c]	$Cu(OTf)_2$	CH_3CN	TMEDA	—	/	/
8	$Cu(OTf)_2$	DMSO	TMEDA	—	45	9
9[c]	$Cu(OTf)_2$	DMF	TMEDA	—	10	/
10[c]	$Cu(OTf)_2$	CH_3OH	TMEDA	—	/	/
11[c]	$Cu(OTf)_2$	H_2O	TMEDA	—	/	/
12[c]	$Cu(OTf)_2$	DMSO	1,2-Ethanediamine	—	/	/
13[c]	$Cu(OTf)_2$	DMSO	*N*,*N*′-Dimethyl-1,2-ethanediamine	—	/	/
14[c]	$Cu(OTf)_2$	DMSO	Cyclohexane-1,2-diamine	—	/	/
15[c]	$Cu(OTf)_2$	DMSO	DABCO	—	28	/
16[c]	$Cu(OTf)_2$	DMSO	1,10-Phenanthroline	—	/	/
17[c]	$Cu(OTf)_2$	DMSO	DABCO	Et_3N/K_2HPO_4	44	/
18[c,d]	$Cu(OTf)_2$	DMSO	DABCO	Et_3N/K_2HPO_4	85	/

[a] Unless otherwise indicated, the reaction conditions were as following: compound **1** (1 equiv), compound **2** (2 equiv), copper source (20 mol %), ligand (20 mol %), additive (2 equiv), 2 mL solvent, rt, air, 5 h.
[b] Isolated yields.
[c] Compound **3** or **4** is trace.
[d] Under 50 °C.

Table 2
Expansion of the C-6 substituted pyridin-2(1*H*)-one



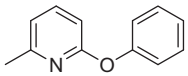
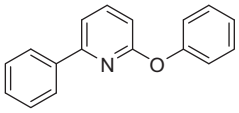
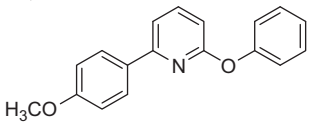
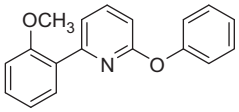
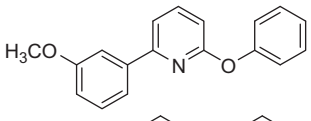
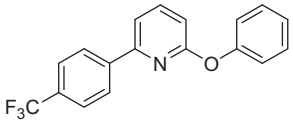
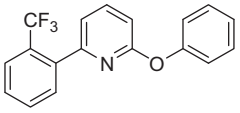
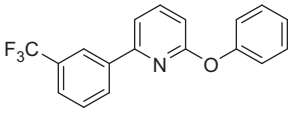
Entry	Product	Yield[a] (%)
1		65
2		74
3		40
4		50
5		61
6		58

Table 2 (*continued*)

Entry	Product	Yield[a] (%)
7		50
8		81

General reaction conditions: 0.2 mmol of 2-hydroxypyridines, 0.4 mmol of phenylboronic acid, 0.04 mmol of $Cu(OTf)_2$ 0.04 mmol of triethylenediamine, 0.4 mmol Et_3N, 0.4 mmol of K_2HPO_4, 2 mL DMSO, 50 °C for 5 h in air.
[a] Isolated yields.

$Cu(II)$ complex, while K_2HPO_4 could avoid the decomposition of phenylboronic acid (**2**) to some extent. Thus, addition of Et_3N and K_2HPO_4 into the reaction was attempted (entry 17), which gave a slightly improved yield (44%). When the temperature was elevated to 50 °C, the yield was improved up to 65% (entry 18). Unfortunately, the yield could not be further improved because of the inevitability of the decomposition of phenylboronic acid.

Finally, the optimal conditions for the selective O-arylation[18] were determined as following: 20 mol % of $Cu(OTf)_2$ as the catalyst, 20 mol % of DABCO as the ligand, Et_3N as the base and K_2HPO_4 as the additives and at 50 °C for no more than 5 h.

With the method[18] in hand, a series of C-6 substituted pyridin-2-ones was subjected to the coupling reaction with phenylboronic acid (**2**), as illustrated in Table 2, O-arylated compounds were obtained in moderate to good yields (40–81%). It was obvious that the C-6 substituent could influence the yield of this reaction. The