



A facile synthesis of novel tricyclic 4-pyridones



Buzhe Xu^a, Zhanling Cheng^{b,*}, Lei Fu^{a,*}

^aSchool of Pharmacy, Shanghai Jiao Tong University, Shanghai 200240, China

^bRoche Innovation Center Shanghai, 720 Cailun Road, Building 5, Pudong Shanghai 201203, China

ARTICLE INFO

Article history:

Received 26 September 2014

Revised 21 October 2014

Accepted 3 November 2014

Available online 10 November 2014

Keywords:

4-Pyridone

Tricyclic

Intramolecular Heck coupling

Palladium bromide

ABSTRACT

A new and efficient synthesis of tricyclic 4-pyridone analogs through the intramolecular Heck coupling cyclization was described. This reaction features mild conditions and good functional group tolerance allowing for the preparation of several novel tricyclic 4-pyridone analogs.

© 2014 Elsevier Ltd. All rights reserved.

Fused nitrogen-containing heterocycles are structural motifs of numerous natural products possessing important biological activities (e.g., alkaloids). These compounds are also extensively explored in the pharmaceutical and biotechnology industry (e.g., morphine, vinca alkaloids). Among these molecules, polycyclic 4-pyridone is one example showcased in several approved drugs for treatment of HIV (e.g., Elvitegravir and Dolutegravir).¹ As such, synthetic methodologies leading to polycyclic 4-pyridone analogs have attracted much attention. Specifically, the synthesis of polycyclic 4-pyridone compounds generally requires to construct the 4-pyridone ring. However, most of these methods involved harsh reaction conditions such as strong acidic condition and heating, subsequently leading to limited functional group tolerance and substrate scope.² With the advent of transition metal catalyzed coupling reactions, recently several publications merged using transition metal-catalyzed preparation of polycyclic 4-pyridones.³

In a research project toward developing robust and convenient method to prepare these compounds with broad functional group tolerability, another methodology leveraging the intramolecular Heck coupling reaction was envisioned to prepare tricyclic 4-pyridone analogs. Heck coupling reactions are playing an important role in the preparation of natural products.^{4–6} Particularly, intramolecular Heck coupling reactions are widely used in the construction of macrocyclic rings present in several drugs and natural products.^{7–9} In our case of 4-pyridone compounds, **C(3)** as an intrinsically more reactive position has been reported to be easily

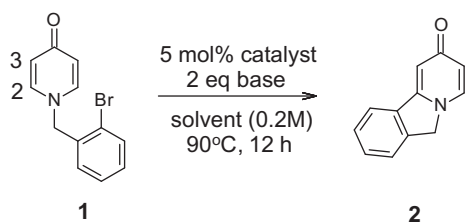
functionalized by electrophilic reagents such as NBS, nitric acid, and other similar reagents.^{2,12} Recently it has been reported that 4-pyridone analogs could also be functionalized by transition metal catalyzed reaction and direct metalation followed by trapping with electrophiles.¹⁰ On the other hand, due to its intrinsic inactive nature, the **C(2)** functionalization of 4-pyridone has not been extensively explored.¹¹ Herein, we report our approach to prepare tricyclic 4-pyridone compounds through intramolecular Heck reaction with embedded 4-pyridones at the **C(2)** position. This method has excellent functional group compatibility and thus is amenable to a broad substrate scope in typically good to excellent yields.

Our study began with a model reaction shown in [Table 1](#). In order to optimize the reaction, a series of conditions were screened, and the results are listed in [Table 1](#). With DMA as solvent, a range of Pd catalysts and base combinations were firstly screened. It was found that base was important for the reaction. Generally alkaline salts of acetate ([Table 1](#), entries 1, 8–10) were beneficial whereas silver acetate, cesium carbonate, and potassium phosphate ([Table 1](#), entries 2, 3, 14) were not suitable for this reaction. Furthermore, the presence of certain phosphine ligands and using ligand coordinated Pd(0) catalysts were deleterious to the reaction compared to Pd(II) catalysts ([Table 1](#), entries 5–7). It is also interesting to note that PdCl₂ and PdBr₂ showed superior catalytic activity although Pd(OAc)₂ was the most frequently used catalyst for the Heck reaction. Regarding the choice of solvents, both DMF and DMA were good reaction media without difference in yields, whereas other solvents either gave no reaction or reduced yields ([Table 1](#), entries 16–19). The best yield was obtained when the reaction was carried out in DMA with Pd(II)

* Corresponding authors. Tel.: +86 21 38954910x3116.

E-mail addresses: zhanling.cheng@roche.com (Z. Cheng), leifu@sjtu.edu.cn (L. Fu).

Table 1
Examination and optimization of reaction conditions



Entry	Catalyst	Base	Solvent	Yield ^d (%)
1	Pd(OAc) ₂	KOAc	DMA	65
2	Pd(OAc) ₂	AgOAc	DMA	N.R. ^b
3	Pd(OAc) ₂	CS ₂ CO ₃	DMA	N.R.
4	Pd(OOCCF ₃) ₂	KOAc	DMA	N.R.
5	PdCl ₂ (PPh ₃) ₂	KOAc	DMA	42
6	Pd(PPh ₃) ₄	KOAc	DMA	3
7	Pd ₂ (dba) ₃	KOAc	DMA	Trace
8	PdCl ₂	KOAc	DMA	90
9	PdBr₂	KOAc	DMA	95
10	PdBr ₂	NaOAc	DMA	88
11	PdBr ₂	K ₂ CO ₃	DMA	53
12	PdBr ₂	Et ₃ N	DMA	Trace
13 ^c	PdBr ₂	KOAc	DMA	98
14	PdBr ₂	K ₃ PO ₄	DMA	Trace
15 ^c	PdBr ₂	KOAc	DMA	N.R. ^d
16 ^c	PdBr ₂	KOAc	CH ₃ CN	27
17 ^c	PdBr ₂	KOAc	Dioxane	Trace
18 ^c	PdBr ₂	KOAc	DMF	90
19 ^c	PdBr ₂	KOAc	Toluene	29
20	—	KOAc	DMA	N.R.
21	PdBr ₂	—	DMA	N.D. ^e

Reaction conditions: 1-(2-bromobenzyl)pyridin-4(1H)-one (0.4 mmol), catalyst, and base were dissolved in each solvent (2.0 mL), 90 °C, 12 h.

The row in bold was the optimal condition.

^a Determined by LC-MS.

^b N.R. = no reaction.

^c 5 mol % TBAB was added.

^d Open to air atmosphere.

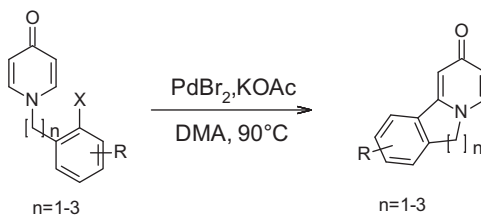
^e N.D. = no desired product.

bromide as the catalyst, and potassium acetate as the base (Table 1, entry 9). The screening of the conditions also showed that both the Pd(II) catalyst and the acetate base were necessary for the reaction (Table 1, entries 20, 21), and the reaction failed when conducted in air. Tetrabutylammonium bromide (TBAB) was reported to prevent the generation of palladium black and make the catalytic system more stable.¹³ In our case, it was shown the reaction with the presence of TBAB did not show significant difference compared with no TBAB addition (Table 1, entry 13 vs entry 9). Hence, this optimized condition (Table 1, entry 9)¹⁴ was used as the standard condition for the subsequent studies.

With this optimized condition in hand, we started to explore the scope of this reaction. A series of *N*-bromophenyl substituted 4-pyridones underwent smooth cyclization and the results are summarized in Table 2. Monitored by LC-MS, this reaction proceeded smoothly. This reaction also showed very good functional group tolerance. It can be seen in Table 2 that both electron-withdrawing groups and electron-donating groups were tolerated under reaction conditions. It is also noteworthy that a chloro substituent remained intact under the reaction conditions, which provided a useful handle for further transformation of the compound (Table 2, entry 6). For the six membered ring closure, a substrate with electron-withdrawing groups gave higher yields than the one with electron-donating groups (Table 2, entry 9 vs entry 10). Importantly, this intramolecular Heck coupling reaction can even be used to afford seven-membered ring-containing products (Table 2, entry 11). Finally we found heteroaryl bromides also worked well for this cyclization (Table 2, entry 12, 13).

After the exploration of a variety of substitutions on the bromophenyl, we also screened the partner of the Heck coupling reaction and the results are shown in Table 3 and Table 4. It was shown that this reaction proceeded smoothly for both benzopyridone (compound 19) and substituted pyridones. For substituted pyridines at the position adjacent to ketone moiety, the reaction worked well for both electron-donating groups and electron-withdrawing groups. In several cases, a mixture of regiomers was obtained, and the isomer structures can be easily deduced by the coupling

Table 2
Intramolecular Heck coupling of pyridone with substituted phenyl ring^a



Entry	Products	X	Yield ^b (%)	Entry	Products	X	Yield ^b (%)
1		Br	72	8		Br	60
2			55	9			85
3		Br	50	9		Br	85

(continued on next page)

Download English Version:

<https://daneshyari.com/en/article/5268558>

Download Persian Version:

<https://daneshyari.com/article/5268558>

[Daneshyari.com](https://daneshyari.com)