



Palladium-catalyzed C-H formylation of electron-rich heteroarenes through radical dichloromethylation

Yan Bao, Jian-Yong Wang, Ya-Xuan Zhang, Yan Li, Xi-Sheng Wang*

Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 230026, PR China

ARTICLE INFO

Article history:

Received 7 June 2018

Revised 28 June 2018

Accepted 3 July 2018

Available online 4 July 2018

Keywords:

Palladium-catalyzed

Formylation

Radical

Heteroarenes

ABSTRACT

A novel palladium-catalyzed C-H formylation of electron-rich N-, O-, and S-containing heteroarenes has been developed. The key to success is that the commercially available BrCHCl_2 was used as a stoichiometric carbonyl source. Mechanistic investigations indicated that different from the known Reimer-Tiemann reaction, this net C-H formylation proceeded through an electrophilic radical-type path.

© 2018 Elsevier Ltd. All rights reserved.

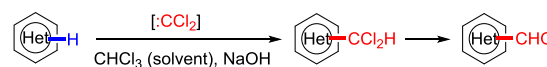
Introduction

To synthesize complex molecules in an efficient and quick manner still remains a big challenge in organic synthesis. Of significant interest is to develop novel methods for facile functionalization of key motifs in a step-economical fashion [1,2]. As one of the most important and widely existing skeletons in the biologically active molecules and drugs, the rapid and efficient functionalization of heteroarenes using readily available reagents is always the core field of organic synthesis [3]. Accordingly, the direct C-H formylation of heteroarenes in a chemoselective and regioselective manner has attracted great attention in the past decades, for the resultant heteroaryl aldehydes could readily undergo various transformations to construct diverse heteroaryl derivatives for further synthesis of complex molecules [4]. Regardless of whether a number of existing traditional methods, including Reimer-Tiemann [5], Vilsmeier-Haack [6], Gattermann-Koch [7], Rieche [8] and Duff [9] reactions, have been developed for direct formylation of heteroarenes, their utilities are still hampered by the requirement of harsh conditions (high temperature, strong bases or acids) and lack of functional group tolerance.

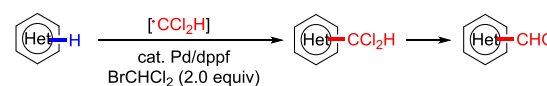
To address these issues, the development of readily available and environmentally benign formylating agents has long been realized as a powerful strategy for facile synthesis of heteroaryl aldehydes [10]. As a result, inspired by the pioneering work of Ru-catalyzed oxidative coupling from Su and coworkers [11], Cu

[12], $n\text{-Bu}_4\text{NI}$ [13] and visible-light photoredox catalysis [14] were developed soon after, while they only focused on the indole C-3 formylation. The key tactic was the use of novel carbonyl sources, such as *N*-methyl aniline, TMEDA and DMSO, in which the C-N or C-S bonds were cleaved through the formation of iminium ion or sulfur ylide. Known as Reimer-Tiemann reaction, the most widely recognized formylating agent so far was still chloroform, which could generate dichloromethyl carbene in situ with the help of sodium hydroxide and then directly insert into the C-H bonds of heteroarenes [15]. However, this transformation was relatively inefficient because of the side reaction of ring expansion, and could not tolerate functional groups which were sensitive to strong base [5c]. Different from this known dichloromethyl carbene pathway, we conceived that single-electron reduction of BrCHCl_2 by transition-metal catalyst could generate the dichloromethyl radical [16] to attack heteroarene, is affording the dichloromethylated intermediate and then give the aldehyde after the following

a) Reimer-Tiemann reaction: Insertion of dichloromethyl carbene into C-H bond



b) This work: Radical dichloromethylation



Scheme 1. C-H formylation of heteroarenes using XCHCl_2 as carbonyl sources.

* Corresponding author.

E-mail address: xswang77@ustc.edu.cn (X.-S. Wang).

hydrolysis. Herein, we report a novel palladium-catalyzed C–H formylation of electron-rich *N*-, *O*- and *S*-containing heteroarenes, using commercially available BrCHCl₂ as a stoichiometric carbonyl source. Mechanistic investigations indicated that different from the known Reimer-Tiemann reaction, this net C–H formylation proceeded through an electrophilic radical-type path (Scheme 1).

Results and discussion

Our study commenced with *N*-methyl-3-phenylindole (**1a**) as the pilot substrate and bromodichloromethane (BrCHCl₂) as the formylating agent in the presence of catalytic amounts of Pd(OAc)₂ (10 mol%) and dppf (10 mol%) in CH₃CN at 60 °C. To our delight, the desired aldehyde **2a** was obtained in 8% yield when sodium trifluoroacetate was used as the base (Table 1, entry 4). In contrast, organic bases (entries 5–7) and some inorganic bases (entries 1–3, 8–9) gave only trace amount of the product. Of note was that acetal **2aa**, which could be transformed to **2a** after a simple acid-promoted deprotection, was furnished as the second product accompanying with 7% yield when K₃PO₄·3H₂O was used (entry 1). Considering that Ag(I) could be used as a promoter to activate the C–Br bond in BrCHCl₂ or as a scavenger

of in situ-generated bromide [17], a number of silver salts had been carefully investigated. Remarkably, the reaction yield was significantly improved with addition of AgOAc and Ag₂CO₃ into the catalytic system (entries 10–11). We surmised that the silver salts might play a crucial role to facilitate the removal of bromide anion rather than an oxidant. To test this hypothesis, other normally used oxidants, including K₂S₂O₈, BQ and Cu(OAc)₂, have been investigated, but all giving almost none of the product (entries 12–14). Then we survey the ligands, which play an important role in the Pd-catalyzed system. The reaction was inhibited by most ligands (entries 15–16, see details in the SI). In view of the instability of acetal **2aa**, to further improve the yield, Ac₂O was added as a stabilizer in the reaction, which resulted in a higher combined yield of **2a** and **2aa** (entry 18).

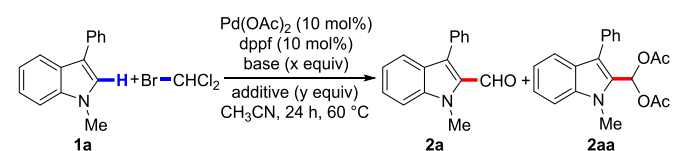
Finally, the careful survey concerning the amount of K₃PO₄·3H₂O and AgOAc (or Ag₂CO₃) identified the optimal conditions in 95% yield, after a simple workup with 3 N HCl (entries 19–20). The efficiency of this reaction was reduced by using the Pd(0) catalyst to instead of Pd(OAc)₂ (entries 21–22).

With the optimized conditions in hand, the substrate scope of this transformation were next examined. A variety of 3-substituted indoles were found to undergo direct C–H formylation smoothly, affording the desired products in moderate to excellent yields (Table 2). Indeed, changing the protecting group of the nitrogen atom from Me to other alkyl groups, such as Et and Bn, had negligible effect on the yields (**2b** and **2c**). Unprotected 3-methyl indole was also formylated smoothly with a relatively low yield (42%, **2d**), presumably due to the possible catalyst deactivation caused by coordination of the free amine with the palladium complex. All indoles bearing both phenyl groups and primary or secondary alkyl groups at the C-3 position proved to be effective substrates for this transformation (**2e–g**). A variety of substituents on the aryl ring of indoles, including both electron-donating groups, such as Me and OMe, and weak electron-withdrawing groups, such as F, Cl and Br, were well tolerated in this catalytic system (**2h–q**).

To demonstrate whether this method could be extended to substrates beyond substituted indoles, we turned our attention to other electron-rich heteroarenes. Unsurprisingly, *N*-methyl pyrroles, a closely related *N*-heteroarene to indole, furnished the formylated products in moderate to good yields even with electron-withdrawing groups on their heteroaryl rings (**4a–d**). Oxygen- and sulphur-containing heteroarenes, including various furan and thiophene derivatives with different functional groups, also were compatible with this formylating system in acceptable yields. In some cases, to achieve higher yields, 3.0 equiv of BrCHCl₂ were required, possibly because of the relatively low reactivity of such heteroarenes to capture the dichloromethyl radical. A range of functional groups including Me, Et, OMe, OBn, Br, CO₂Et, Ac and Ph on the furan and thiophene rings were well tolerated.

To gain some insights into the mechanism of this transformation, a series of control experiments were carried out accordingly. First, we attempted to perform the reaction in the presence of 1.0 equiv of TEMPO as a free radical scavenger. The reaction was completely quenched and a dichloromethyl adduct of TEMPO was detected by GC–MC analysis (Scheme 2, Eq. (1)). This observation indicated the reaction might proceed via a possible radical pathway. To strengthen this hypothesis, 1.0 equiv of butylated hydroxytoluene (BHT) was added into the standard conditions, in which a radical-trapping product **6** was afforded (Eq. (2)), which showed that a dichloromethyl radical was involved in the catalytic cycle. While the isolated acetal **2aa** could readily convert to the final aldehyde in 3 N HCl (eq 3), to elucidate the process of this C–H formylation, the subsection of aldehyde **2a** into the standard conditions gave none of **2aa** at all (Scheme 2, Eq. (4)). This result did reveal that the acetal **2aa** served as the key intermediate from dichloromethylated heteroarenes to the aldehyde products.

Table 1
Optimization of reaction conditions^a



Entry	Base (equiv)	Additive (equiv)	2a/2aa Yield ^b /%
1	K ₃ PO ₄ ·3H ₂ O (1.0)	–	6/7
2	K ₃ PO ₄ (1.0)	–	5/4
3	K ₂ HPO ₄ (1.0)	–	Trace
4	CF ₃ COONa (1.0)	–	8/0
5	DBU (1.0)	–	Trace
6	Et ₃ N (1.0)	–	Trace
7	DABCO (1.0)	–	Trace
8	NaOH (1.0)	–	Trace
9	KOH (1.0)	–	5/0
10	K ₃ PO ₄ ·3H ₂ O (1.0)	AgOAc (2.0)	63/7
11	K ₃ PO ₄ ·3H ₂ O (1.0)	Ag ₂ CO ₃ (2.0)	53/5
12	K ₃ PO ₄ ·3H ₂ O (1.0)	K ₂ S ₂ O ₈ (2.0)	Trace
13	K ₃ PO ₄ ·3H ₂ O (1.0)	BQ (2.0)	n.r.
14	K ₃ PO ₄ ·3H ₂ O (1.0)	Cu(OAc) ₂ (2.0)	n.r.
15 ^c	K ₃ PO ₄ ·3H ₂ O (1.0)	AgOAc (2.0)	Trace
16 ^d	K ₃ PO ₄ ·3H ₂ O (1.0)	AgOAc (2.0)	Trace
17 ^e	K ₃ PO ₄ ·3H ₂ O (1.0)	AgOAc (2.0)	45/32
18 ^e	K ₃ PO ₄ ·3H ₂ O (1.0)	AgOAc (1.5)	48/48 (81)
19 ^e	K ₃ PO ₄ ·3H ₂ O (1.5)	AgOAc (1.5)	65/28 (95)
20 ^e	K ₃ PO ₄ ·3H ₂ O (1.5)	Ag ₂ CO ₃ (1.5)	71/22 (95)
21 ^f	K ₃ PO ₄ ·3H ₂ O (1.5)	Ag ₂ CO ₃ (1.5)	59/7
22 ^g	K ₃ PO ₄ ·3H ₂ O (1.5)	Ag ₂ CO ₃ (1.5)	43/6
23 ^h	K ₃ PO ₄ ·3H ₂ O (1.5)	AgOAc (1.5)	13/64
24 ⁱ	K ₃ PO ₄ ·3H ₂ O (1.5)	AgOAc (1.5)	4/66

^a Reaction condition: **1a** (0.2 mmol, 1.0 equiv), BrCHCl₂ (2.0 equiv), Pd(OAc)₂ (10 mol%), dppf (10 mol%), CH₃CN (1.0 mL), 60 °C, 24 h.

^b Yield determined by ¹H NMR spectroscopy using CH₂Br₂ as an internal standard; numbers in parentheses were yields of isolated product **2a** after hydrolysis by 3 N HCl.

^c none ligand was used.

^d PPh₃ was used as the ligand.

^e Ac₂O (10.0 equiv) was added as the promoter.

^f Pd(PPh₃)₄ was used.

^g Pd₂(dba)₃ was used.

^h Ac₂O (5.0 equiv).

ⁱ Ac₂O (2.0 equiv), n.r. = no reaction.

Download English Version:

<https://daneshyari.com/en/article/7828438>

Download Persian Version:

<https://daneshyari.com/article/7828438>

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