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Simultaneous dehalogenation and hydrogenation reduction of halogen-heteroaromatic aldehydes

Xi-Bo Chen [a,b], Qiu-Peng Hu [a,b], Qian-Jia Yuan [a,b], Wei Ding [a,b], Jiangmeng Ren [a,*], Bu-Bing Zeng [a,b,c,*]

[a] *School of Pharmacy, East China University of Science and Technology, Shanghai 200237, PR China*
[b] *Shanghai Key Laboratory of Chemical Biology, Shanghai 200237, PR China*
[c] *Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, PR China*

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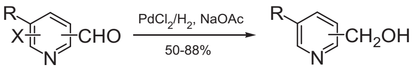
ABSTRACT

Treatment of halogen-heteroaromatic aldehydes with catalytic amount of $PdCl_2$ under atmosphere pressure of hydrogen in base medium (sodium acetate) leads to the corresponding dehalogenated primary alcohols. The reaction system was especially effective for the heteroaromatic compounds bearing aldehyde groups and halides (bromo- or chloro-functions).

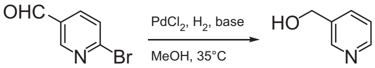
Hydrodehalogenation of aryl halides has been recognized as an important chemical transformation in organic synthesis as well as in the industrial applications.[1] Bromo- or chloro-substituents often severed as excellent blocking groups on aromatic rings.[2] Consequently, a wide variety of hydrodehalogenation reaction systems have been reported to perform this transformation. Among these catalytic systems, the reactions were usually performed with transition metal catalysts (e.g., Ni, Pd) and hydrogen sources (e.g., polymethylhydrosiloxane, H_2, hydrazine).[3,4] However, there were few reports on hydrodehalogenation of heteroaromatic halides due to the proximity of a coordinating heteroatom to the metal center.[5,6] What is more, there were no reports on simultaneous hydrogenation and dehalogenation of halogen-heteroaromatic aldehydes.

When initial hydrodehalogenation of 6-bromonicotinaldehyde was conducted, dehalogenation and hydrogenation of aldehyde to primary alcohol happened simultaneously using catalytic amount of $PdCl_2$ at room temperature under atmospheric pressure of hydrogen in base medium. According to the literature, most hydrogenations of heteroaromatic aldehydes require vast amounts of catalyst, high temperature and/or, high hydrogen pressure.[7] Herein, we wish to develop a general procedure for the $PdCl_2$-catalyzed simultaneous dehalogenation and hydrogenation of halogen-heteroaromatic aldehydes that operated under mild conditions. In addition, this method could be applied to a variety of halogen-heteroaromatic aldehydes (Scheme 1).



Scheme 1. Dehalogenation and hydrogenation of halogen-heteroaromatic aldehydes.

Table 1
Optimization of reaction conditions[a]



1a **2a**

Entry	Cat. (mol %)	Solvent	Base	Yield[b] (%)
1	2	MeOH	NaOAc	42
2	5	MeOH	NaOAc	78
3	10	MeOH	NaOAc	79
4	5	MeOH	DBU	75
5	5	MeOH	Et_3N	53
6	5	MeOH	TMEDA	15
7	5	MeOH	K_2CO_3	Trace
8	5	MeOH	^{t}BuOK	Trace
9	5	MeOH	None	Trace
10	5	^{i}PrOH	NaOAc	34
11	5	Dioxane	NaOAc	7.5

[a] Reaction conditions: 5 mmol of **1a** in given solvent (30 mL), 10 mmol of base, 2–10 mol % $PdCl_2$, H_2 (1 atm), 4 h, 35 °C.
[b] Isolated yield.

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* Corresponding authors. Tel./fax: +86 21 64253689.
E-mail addresses: renjm@ecust.edu.cn (J. Ren), zengbb@ecust.edu.cn (B.-B. Zeng).

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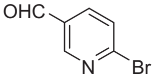
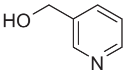
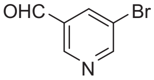
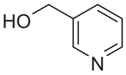
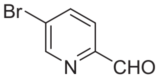
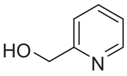
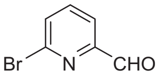
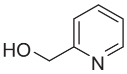
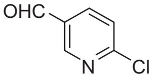
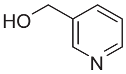
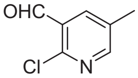
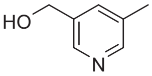
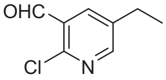
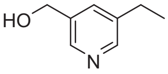
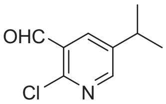
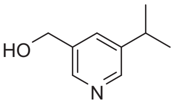
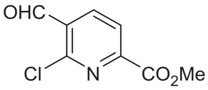
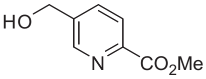
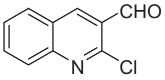
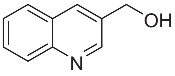
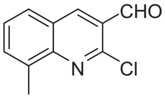
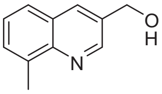
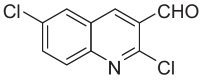
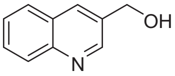
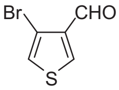
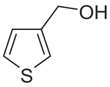
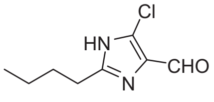
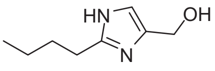
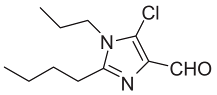
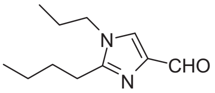
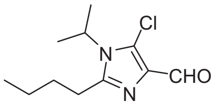
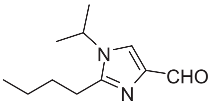
A series of reactions were undertaken to test the effect of catalyst loading amount, bases, and solvents. A preliminary survey of catalytic efficiency with different loadings of catalyst was performed on the model reaction involving 6-bromonicotinaldehyde as the substrate, sodium acetate as the base, and methanol as the solvent under an atmospheric pressure of hydrogen.[8] As shown in

Table 2
One-pot dehalogenation and hydrogenation of halogen-heteroaromatic aldehydes[a]

Entry	Reactant	Product	Cat. (mol %)	Time (h)	Yield[b] (%)
1	 1a	 2a	5	4	78
2	 1b	 2a	5	2	83
3	 1c	 2c	5	4	83
4	 1d	 2c	5	2	0
5	 1e	 2a	5	2	88
6	 1f	 2f	5	2	76
7	 1g	 2g	5	3	87
8	 1h	 2h	5	2	85
9	 1i	 2i	5	3	88
10	 1j	 2j	10	3	84
11	 1K	 2k	10	3	61
12	 1l	 2j	10	2	86
13	 1m	 2m	20	12	50

(continued on next page)

Table 2 (*continued*)

Entry	Reactant	Product	Cat. (mol %)	Time (h)	Yield[b] (%)
14	 1n	 2n	5	12	0
15	 1o	 2o	5	4	71
16	 1p	 2p	5	4	76

[a] Reaction conditions: 5 mmol of substrates in MeOH (30 mL), 10 mmol of sodium acetate, 5–20 mol % $PdCl_2$, H_2 (1 atm), 35 °C.

[b] Isolated yield.

Table 1, the increase in the loading amount of $PdCl_2$ led to the increase of the corresponding products. However, further increase in the amount of catalyst could not continue to improve the yield significantly (Table 1, entries 1–3). Therefore, these data suggested that 5 mol % of catalyst should be the best condition. In order to explore the mechanism of action, the reaction mixture was monitored alone with time. During the model reaction, nicotinaldehyde as a debromination product, was detected first in 30 min. The analytical sample was prepared and its spectral data were found to agree with the commercial available one, which was then reduced into primary alcohol in 4 h. Therefore, the mechanism of this one-pot reaction included the dehalogenation reaction happened first and then the reduction of aldehyde as a final product.

A variety of bases were then examined in the catalytic system. Among these bases, sodium acetate and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) were the most efficient (Table 1, entries 2 and 4). Other bases such as Et_3N, tetramethylethylenediamine (TMEDA), K_2CO_3 and ^{t}BuOK showed a little or no activity at all (Table 1, entries 5–8). At the same time, the reaction was sluggish in the absence of base (Table 1, entry 9). These variations in yields ruled out that the base was not limited to neutralize the generated hydrogen halide. Due to the lower cost and the slightly higher yield, sodium acetate was chosen as the most effective base to further investigate the effect of solvent. Among the tested solvents, methanol was found to be the best (Table 1, entries 2, 10, and 11).

The generality and the limitations of this methodology were demonstrated by subjecting a broad sampling of functionalized substrates to conduct the reactions under the optimized condition as illustrated in Table 2. It is well known that aromatic chlorides are much less reactive than that of aromatic bromides and hence, the dechlorination of aromatic chlorides could not readily be achieved, especially for the heteroaromatic chlorides. In addition, the reduction of heteroaromatic aldehydes to its corresponding primary alcohols often requires harsh reaction conditions. Excitedly, with the presence of the optimized catalyst system, both the reduction of aldehyde group and hydrodehalogenation of halides (bromo- or chloro-functions) took place concurrently in good yields. Heteroaromatic chlorides and bromides behaved similarly.

With the substrates bearing aldehyde group and halides (bromo- or chloro-functions) at the *meta*- or *ortho*-positions of the heterocyclic ring, nearly all the reactions performed well (Table 2, entries 1–3 and 5) except 6-bromopicolinaldehyde, which its corresponding reduced product was not detected (Table 2, entry 4). We also discovered that the presence of additional substituent did not affect the efficiencies of the optimized catalyst system. Substrates with electron-rich (Table 2, entries 6–8) or electron-deficient group on the heteroaromatic ring (Table 2, entry 9) readily reacted under similar conditions to give the corresponding reduced products in high yields ranging from 76% to 88%. At the same time, functional groups, such as methyl ester, were tolerated (Table 2, entry 9).

Meanwhile, other halogen-heteroaromatic aldehydes were investigated under the standard conditions. In order to achieve the similar results, quinoline compounds required higher catalyst loading amount of 10 mol % (Table 2, entries 10–12). Hydrodechlorination of dichloroarenes took place smoothly with this catalyst system to give the corresponding product in excellent yields (Table 2, entry 12). This result exhibited that the present catalyst system was effective not only for heteroaromatic chlorides but also for aromatic chlorides. On the other hand, substituted thiophene afforded a moderate yield though the catalyst loading amount was increased up to 20 mol % and the reaction time became 12 h (Table 2, entry 13). Imidazole-substituted aldehydes were tested as well. The results showed that N-alkylated imidazole compound could only undergo dehalogenation with the aldehyde group remaining, while with the starting material of **1n**, no product was detected (Table 2, entries 14–16). The electron-rich imidazole rings may form complex with $PdCl_2$ which reduced the activity of the catalyst.

In summary, a mild and efficient simultaneous method was developed for the dehalogenation and hydrogenation of halogen-heteroaromatic aldehydes using atmosphere pressure hydrogen. This method generally worked well for a variety of halogen-heteroaromatic aldehydes. The simplicity and the reliability of this method make it an attractive new tool for organic chemists.tpb 2

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.054.

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8. *Typical procedures*: 6-bromonicotinaldehyde (930 mg, 5.0 mmol), NaOAc (820 mg, 10.0 mmol), MeOH (30 mL), and $PdCl_2$ (45 mg) were mixed in a glass bottle capped with a balloon filled with hydrogen. After stirred at 35 °C for 4 h, the mixture was filtered and washed with MeOH. The solvent was removed and the residue was dissolved in water, neutralized with solid $NaHCO_3$, and extracted with ethyl acetate. The organic phase was dried over anhyd Na_2SO_4, and then filtered. The solvent was removed and the residue was subjected to chromatography to yield pyridin-3-ylmethanol (428 mg, 78%).