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Carbon dioxide promoted reductive amination of aldehydes in water mediated by iron powder and catalytic palladium on activated carbon

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ABSTRACT

A mixture of iron powder and catalytic palladium on activated carbon has been developed for reductive amination of various aromatic aldehydes, including 2-pyridinecarboxaldehyde, in water under CO_2 atmosphere. The reversible reaction of CO_2 with water could form carbonic acid and hydrogen transfer from water to Pd(0) took place with the presence of iron powder, leading to formation of high-active Pd hydrides for the reductive amination process. On the other hand, the reaction system could be inherently neutralized by ready removal of CO_2, thus resulting in facile post-processing.

1. Introduction

Preparation of functionalized amines in an effective way has always been necessary especially in medicinal chemistry and modern organic synthesis. In this context, direct reductive amination of carbonyl compounds represents a powerful tool for the preparation of amine derivatives, which generally includes two steps: the formation of imines *via* the reaction of aldehydes or ketones with amines and subsequent hydrogenation [1–3]. Ecological and economic benefits of this kind protocol are obvious since the amount of solvents, reagents and energy consumption would be dramatically reduced compared with the stepwise processes. However, despite being a reaction of proven efficiency, it presents a large drawback related with the handling of hydrogen gas (flammable and explosive). For this reason, numerous alternative reducing agents that are mainly rely on precious metals (*e.g.*, Ir, Pt, Rh, Ru) have been developed, such as active boranes or tin compounds, iso-propanol, formates, silanes, and so-called Hanztsch esters [4–8]. Recently, Beller et al. reported the nanostructured iron-catalyst for the tandem reductive amination between nitroarenes and aldehydes using hydrogen as reductant [9]. While, there is still much room for improvement in terms of environmentally benign hydrogen source and easily operated processes with less expensive and less toxic metals.

The efficient reduction of water for generation of hydrogen is one of the most challenging transformations in chemistry and water is the ultimate hydrogen source, being both safe and plentiful. In the CO_2–H_2O two phase system, water is thought to behave as the terminal hydrogen source with the presence of the reducing metal such as Fe or Zn because the reversible reaction between CO_2 and H_2O could form the carbonic acid with a pH value as low as 3 [10]. And this CO_2/H_2O system could be inherently neutralized by readily remove of CO_2. As an extension of our previous works on the use of *in situ* carbonic acid-promoted organic reactions [11], we herein would like to apply such self-neutralizing acid for the synthesis of various amine derivatives by the direct reductive amination of aldehydes, thus avoiding isolating the imines intermediate (Scheme 1). Pd/C and iron powder mixture in the CO_2/H_2O system has been revealed to be an efficient methodology for the reductive amination process and satisfactory yields of the one-pot formed amines were achieved with facilitated post-processing procedures.

2. Experimental

Aldehydes and amines were purchased from Aladdin Reagent Inc. Pd/C and iron powder was purchased from Alfa Aesar China Co., Ltd. Distilled water and all other reagents were obtained

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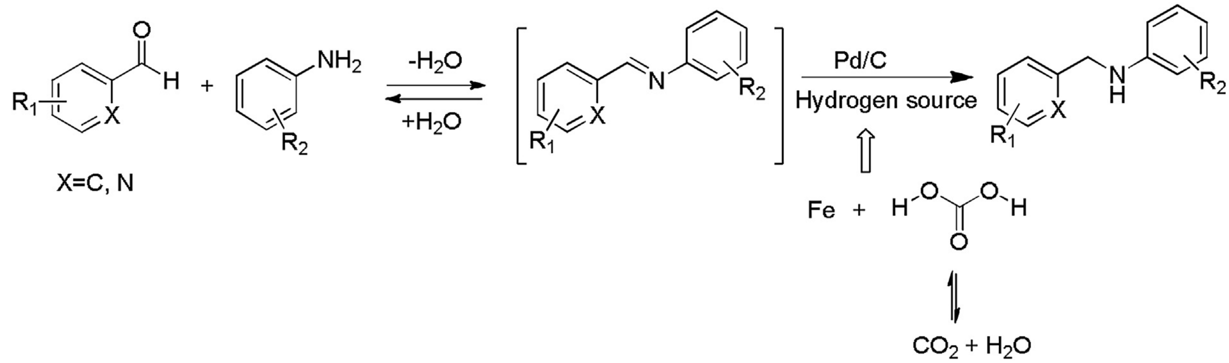
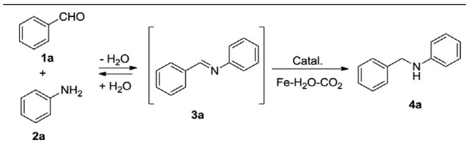


Scheme 1. Pd/C-catalyzed reductive amination of aldehydes with Fe in CO_2/H_2O system.

Table 1
Reductive amination with Fe in CO_2/H_2O system[a].



Entry	Catal.	CO_2 (MPa)	Conv.[b] (%)	Yield (%)	
				3a[b]	**4a**[b]
1	–	8	93	92	–
2	$ZnCl_2$	8	88	84	–
3	$FeCl_2$	8	94	93	–
4	$FeBr_3$	8	58	54	–
5	$RuCl_3$	8	57	53	–
6	$Cu(OTf)_2$	8	50	39	6
7	$RhCl_3$	8	33	26	4
8	$IrCl_3$	8	66	57	4
9	$PdCl_2$	8	92	73	19
10	Pd/C	8	86	50	33
11	$PdBr_2$	8	55	41	11
12	$Pd(OAc)_2$	8	57	50	1
13[c]	Pd/C	8	84	84	–
14	Pd/C	–	88	76	–
15[d]	Pd/C	–	–	–	–

[a] Reaction conditions: benzaldehyde (1.1 mmol, 116.7 mg), aniline (1 mmol, 93.1 mg), catalyst 5 mol%, H_2O (2 mL), Fe (2 mmol, 111.7 mg), 80 °C, 10 h.
[b] Conversion and yield were relative to primary amine and determined by GC with biphenyl as the internal standard.
[c] Without Fe.
[d] H_2 balloon, toluene was detected.

commercially from Tianjin Guangfu Fine Chemical Research Institute and used without further purification. ^{1}H NMR spectra was recorded with a Bruker 400 spectrometer in $CDCl_3$ and $CDCl_3$ (7.26 ppm) was used as the internal reference. ^{13}C NMR was recorded at 100.6 MHz in $CDCl_3$ and $CDCl_3$ (77.0 ppm) was used as the internal reference. GC–MS datas were collected on a Finnigan HPG1800 A. GC analyses were performed on a Shimadzu GC-2014, equipped with a capillary column (RTX-17, 30 m × 0.25 μm) using a flame ionization detector.

2.1. *Reduction amination of aldehydes with Fe powder in CO_2/H_2O*

A mixture of aldehyde (1.1 mmol), amine (1 mmol), Fe (3 mmol, 167.5 mg), Pd/C (Palladium on activated carbon 5% Pd, 106.4 mg), H_2O (3 mL) was placed in a 50 mL stainless steel autoclave equipped with an inner glass tube at room temperature. The vessel was sealed and CO_2 was subsequently introduced into the autoclave, which was then heated under the predetermined reaction temperature for 25 min to reach the equilibration. The final pressure was adjusted to the desired pressure by introducing the correct amount of CO_2. After the reaction was finished, the vessel was cooled within an ice-bath and the pressure was released slowly to atmospheric pressure. The products were diluted with ethyl acetate and analyzed by GC. The residue was purified by column chromatography on silica gel (200–300 mesh, eluting with *n*-hexane and ethyl acetate) to afford the desired product. The isolated products were further identified with NMR spectra and GC–MS, which are consistent with those reported in the literature.

Table 2
Optimization of the reaction parameters[a].

Entry	CO_2 (MPa)	H_2O (mL)	Temp. (°C)	Conv.[b] (%)	Yield **4a**[b] (%)
1	8	2	80	86	33
2	8	3	80	85	45
3	12	3	80	81	17
4	4	3	80	87	34
5[c]	8	3	80	84	52
6[c,d]	8	3	80	93	75

[a] Unless otherwise stated, all the reactions were carried out with 1.1 mmol **1a** and 1.0 mmol **2a** in 2 mL solvent in the presence of Pd/C and Fe, at 80 °C for 10 h.
[b] Conversion and yield were based on primary amines and determined by GC with biphenyl as the internal standard.
[c] Fe (3 mmol, 167.5 mg).
[d] 15 h.