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Highly efficient one pot synthesis of benzimidazoles from 2-nitroaniline and $PhSiH_3$ as reducing agent catalyzed by Pd/C as a heterogeneous catalyst

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ABSTRACT

This work reports an efficient route for the synthesis of benzimidazole from o-nitroaniline in the presence of carbon dioxide atmosphere, $PhSiH_3$ as a reducing agent catalyzed by Pd/C as a catalyst. Benzimidazoles have become the focus of organic chemists, as benzimidazole is an important intermediate in medicinal chemistry. We have developed more efficient route for the synthesis benzimidazole and various substituted benzimidazoles have been synthesized in good to excellent yield. The TBD (1,5,7-Triazabicyclo [4.4.0] dec-5-ene) is selected as a base as it promotes the CO_2 insertion. Benzimidazoles were synthesized through reduction of nitro group followed by cyclization of amine using CO_2 as a carbon source. Moreover, the Pd/C catalyst can be recycled up to five recycle run without significant changes in the yield of the product.

Introduction

The capture and utilization of CO_2 is an efficient method to mitigate the rising concern of global warming related to CO_2 emission. The utilization of carbon dioxide (CO_2) has been increasing interest as the requirement of sustainable development and environmental concerns [1–4]. The CO_2 is generally used as a renewable, green and economical C1 source and the chemical transformation of CO_2 has been extensively studied. A variety of value-added chemicals such as formamides [5,6], formic acids [7], carbonates [8,9], carbamates [2], methanol [10], benzimidazole [11,12] were synthesized by the formation of C—N, C—O, C—H, and C—N bond. Generally, a catalyst is required for CO_2 conversion due to the thermodynamic and kinetic stability of CO_2, and many studies have been developed for efficient conversion of CO_2.

Benzimidazoles and its derivatives are vital intermediates and widely used in synthesizing important pharmaceutical compounds. Benzimidazoles are synthesized via condensation reactions of o-phenylenediamine with formic acid or its derivatives (esters, nitriles) in the presence of strong acidic conditions with relatively high temperatures or under microwave irradiation [13,14].

Literature shows that there are only a few reports available on the direct conversion of o-nitroaniline to benzimidazole in the presence of CO_2 atmosphere. Hao et al. reported Au/TiO_2 catalyst for the synthesis of benzimidazoles from o-nitroaniline and H_2 as a reducing agent in the presence of CO_2 (CO_2 and H_2 = 8 MPa) at 100 °C for 12 h (Scheme 1a) [15]. Recently, the synthesis of formamides and benzimidazoles from amines, nitrobenzene and o-nitroaniline catalyzed by Ru@PSIL has been reported (Scheme 1b) [16]. Previously, *N*-formylation of amines was obtained by using Pd-NC-800 catalyst in presence of 7 MPa pressure (H_2:CO_2 – 4:3) at 130 °C [17]. It is an interesting route for the direct synthesis of benzimidazole from nitroaniline with CO_2 and silane as a reducing agent. Previously hydrogen gas was used as a reducing agent [15]. H_2 is one of the clean source of energy and economical hydrogen source but require high pressure and temperature, handling of H_2 at high temperature limits its broad application. Hydrosilanes and H_2 having similar reduction potential (H_2 and Si-H bond). The Si-H bond kinetically more active due to its lower bond dissociation energy and polarity. Additionally, hydrosilanes are air-stable and less moisture sensitive compare to boron hydride. TBD (1,5,7-Triazabicyclo [4.4.0] dec-5-ene) was selected as a base as it activates CO_2 and helps to insertion of CO_2. TBD is the most common super base used in organic synthesis due to its high Pka value [18].

There are only a few reports available to synthesize benzimidazoles from o-nitroaniline and CO_2 as a carbon source in literature.

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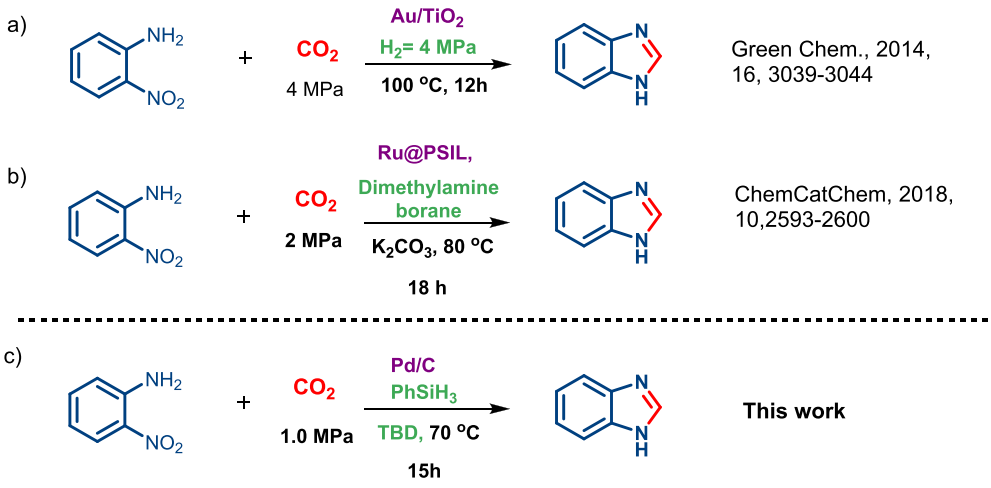


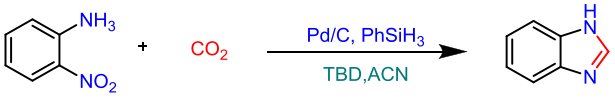
Scheme 1. Comparison of previous reports of synthesis of benzimidazole from o-nitroaniline and CO_2.

There is a need to develop a more efficient, simple and sustainable route for the synthesis of benzimidazoles from o-nitroaniline. Herein, we report the efficient synthesis of benzimidazole directly from ortho nitroaniline, phenyl silane as a reductant, ACN (acetonitrile) as a solvent in the presence of CO_2 atmosphere at 70 °C for 15 h.

Result and discussion

We have selected 2-nitroaniline with CO_2 and different reducing agents as a model reaction for the synthesis of benzimidazole. We examined various parameters such as a solvent, temperature, pressure, time, CO_2 pressure, base, palladium catalyst, etc. Several solvents, including polar and non-polar solvents were studied for the synthesis of benzimidazole out of which Acetonitrile (ACN) and DMSO gave the 90 and 88% yield and ACN selected as a solvent for the further experiments (Table 1, entries 1–5). This is due to the excellent solubility of carbon dioxide in the polar aprotic solvent (ACN and DMSO). Next, we screen various palladium catalysts such as $PdCl_2$ and $Pd(OAC)_2$ gave the lower yield compared to Pd/C catalyst (Table 1, entries 6, 7 and 1). Furthermore, we examined other silanes such as $PhSiH_3$ and PMHS (Polymethylhydrosiloxane). $PhSiH_3$ and PMHS gave an excellent yield compare to Et_3SiH (Table 1, entries 8 and 9). $PhSiH_3$ is selected as a reducing agent for further experiments. Next, the effect of various bases has been

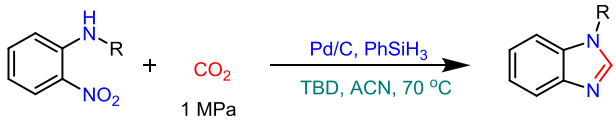
Table 1
Optimization study.

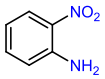
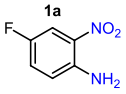
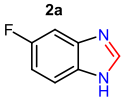
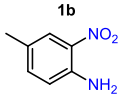
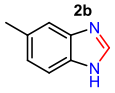
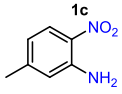
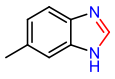
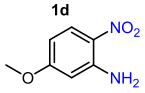
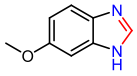
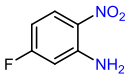
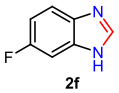
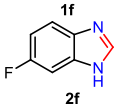
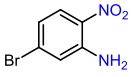
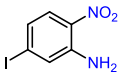
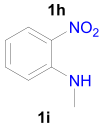
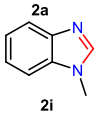
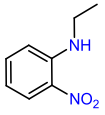
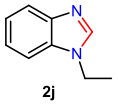
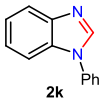
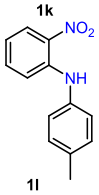
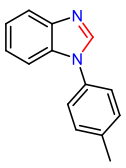
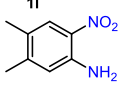
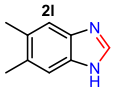


Entry	Solvent	Reducing agent	Catalyst	Base	CO_2 (MPa)	Temperature (°C)	Time (h)	Yield[b] (%)
Effect of Solvent								
1	Toluene	Et_3SiH	10% Pd/C	TBD	2	80	20	–
2	1,4-dioxane	Et_3SiH	10% Pd/C	TBD	2	80	20	35
3	CH_3CN	Et_3SiH	10% Pd/C	TBD	2	80	20	67
4	ACN	Et_3SiH	10% Pd/C	TBD	2	80	20	78
5	DMSO	Et_3SiH	10% Pd/C	TBD	2	80	20	72
Effect of other Palladium catalyst								
6	ACN	Et_3SiH	$PdCl_2$	TBD	2	80	20	35
7	ACN	Et_3SiH	$Pd(OAC)_2$	TBD	2	80	20	62
Effect of reducing agent								
8	ACN	$PhSiH_3$	10% Pd/C	TBD	2	80	20	92
9	ACN	PMHS	10% Pd/C	TBD	2	80	20	86
Effect of Base								
10	ACN	$PhSiH_3$	10% Pd/C	DBU	2	80	20	76
11	ACN	$PhSiH_3$	10% Pd/C	DMAP	2	80	20	54
12	ACN	$PhSiH_3$	10% Pd/C	DABCO	2	80	20	49
Effect of Temperature								
13	ACN	$PhSiH_3$	10% Pd/C	TBD	2	70	20	92
14	ACN	$PhSiH_3$	10% Pd/C	TBD	2	60	20	70
Effect of Time								
15	ACN	$PhSiH_3$	10% Pd/C	TBD	2	70	15	88
16	ACN	$PhSiH_3$	10% Pd/C	TBD	2	70	10	67
Effect of Pressure								
17	ACN	$PhSiH_3$	10% Pd/C	TBD	1	70	15	89
18	ACN	$PhSiH_3$	10% Pd/C	TBD	0.5	70	15	61
Effect of $PhSiH_3$ loading								
19[c]	ACN	$PhSiH_3$	10% Pd/C	TBD	1	70	15	91
20[d]	ACN	$PhSiH_3$	10% Pd/C	TBD	1	70	15	63

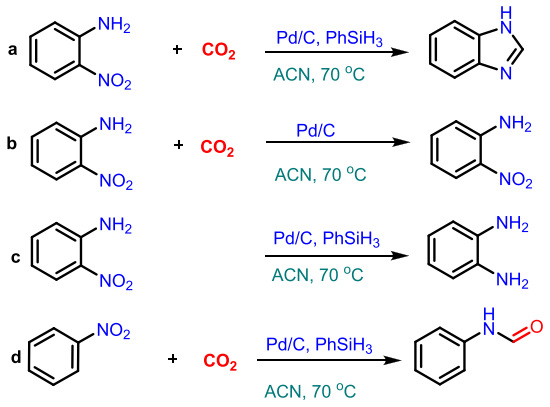
a – Reaction condition: o-nitroanlines (0.5 mmol), catalyst (10 mg, 0.01 mmol Pd), $PhSiH_3$ (4 equi.), Base (5 mol%), ACN (7 mL), Temperature (70 °C) for 15 h. b – GC and GCMS Yield. c – $PhSiH_3$ (3 equi.). d – $PhSiH_3$ (2 equi.).

Table 2
Substrate study.[a]



Entry	Substrate	Product	Yield[b] (%)
1			94
2	1a 	2a 	85
3	1b 	2b 	95
4	1c 	2c 	94
5	1d 	2d 	92
6	1e 	2e 	88
7	1f  2f		07 (78)[c]
8		1g 	82
9	1h  1i	2a  2i	95
10		 2j	94
11	1j 	 2k	72
12	1k 		70
13	1l  1m	2l  1n	84

a – Reaction condition: Substrate (1 mmol), catalyst (10 mg, 0.01 mmol of Pd), $PhSiH_3$ (3 equi.), TBD (5 mol%), CO_2 (1 MPa), ACN (7 mL), Temperature (70 °C) for 15 h. b – Isolated yield (%). c – benzimidazole



Scheme 2. Controlled experiments.

studied. DBU, DABCO, DMAP gave the lower yield compare to TBD (Table 1, entries 10–12). Next, the effect of temperature was studied from 80 to 60 °C and 70 °C temperature is optimum for this reaction (Table 1, entries 13 to 14). Then, the effect of time was performed and 15 h of reaction time was gave the 88% yield of benzimidazole. Further decrease in the reaction time to 10 h yield of benzimidazole was decreased (Table 1, entries 15 to 16). After this, the influence of CO_2 pressure was also examined and 1.0 MPa of CO_2 pressure was sufficient to give 89% yield of benzimidazole, further reducing the CO_2 pressure to 0.5 MPa significant decrease in the yield of benzimidazole was observed (Table 1, entries 17 to 18). Next, the influence of $PhSiH_3$ loading was also examined, three equivalents of $PhSiH_3$ is enough to obtained benzimidazole in excellent yield (Table 1, entries 19 to 20).

The final optimized reaction condition is 2-nitroaniline (0.5 mmol), CO_2 (1 MPa), Pd/C (10 mg, 0.01 mmol of Pd), $PhSiH_3$ (3 equi.), TBD (5 mol%), ACN (7 mL) at 70 °C for 15 h.

Several o-nitroanilines were evaluated by using optimized reaction conditions. The o-nitroanilines bearing electron-withdrawing and -donating groups were well tolerated except bromo and iodo substituted benzimidazole under the optimized reaction condition to obtain various benzimidazoles in good to excellent yields (Table 2). O-nitroaniline gave the benzimidazole in 94% yield (Table 2, entry 1). Furthermore, the steric effect on o-nitroaniline was also examined. O-nitroanilines having donating groups (methyl, methoxy groups) gave the excellent yield of the corresponding benzimidazole compare to the withdrawing substrate (Table 2, entries 2 to 6). When we performed the reaction with 5-bromo-2-nitroaniline gave the corresponding benzimidazole only 7% and benzimidazole 78% (Table 2 entry 7). Then we

Mechanism:

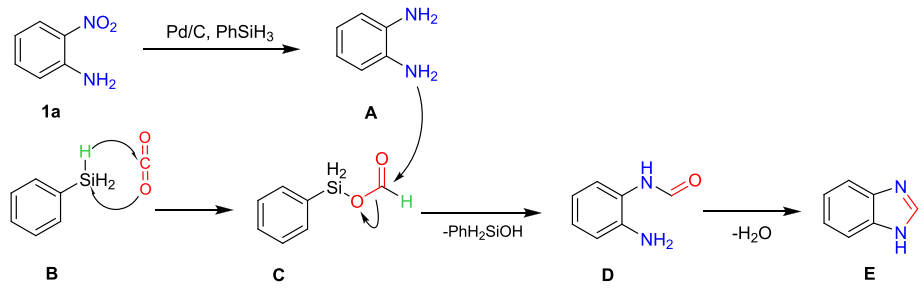


Fig. 1. Plausible reaction mechanism based on the previous report and experimental data.

Fig. 2. Recyclability of Pd/C for the synthesis of benzimidazole.

performed a reaction with 4-iodo-2-nitroaniline as a substrate gave only benzimidazole instead of 5-iodo-1H-benzimidazole (Table 2 entry 8). Additionally, *N*-substituted nitroaniline having methyl and ethyl groups (Table 2, entries 9 and 10) gave the excellent yield compare to *N*-substituted nitroaniline having phenyl group (Table 2, entries 11 and 12), this is due to the steric hindrance of the phenyl group. Next, 4,5-dimethyl benzimidazole was also synthesized in good yield from 4,5-dimethyl-2-nitroaniline (Table 2 entry 13).

Next, we performed controlled experiments (Scheme 2). First, we tried the reaction with an optimized reaction condition and benzimidazole obtained as a product (Scheme 2a). Then we performed the reaction without reducing agent ($PhSiH_3$), and no reduction of the nitro group, as well as CO_2 insertion was observed (Scheme 2b). Next, the reaction was performed without CO_2; only the reduction of the nitro group was observed (Scheme 2c). To confirm the *N*-formamide as an intermediate after CO_2 insertion, we performed the reaction with nitrobenzene instead of o-nitroaniline and formanilide was observed in good yield (Scheme 2d).

On the basis of controlled experiments and previous reports, a plausible reaction mechanism has been proposed for the synthesis of benzimidazole from nitroaniline, CO_2 and $PhSiH_3$ as a reducing agent and Pd/C as a catalyst (Fig. 1) [19–22]. Intermediate A is obtained from ortho nitroaniline by in situ reduction of nitro group using Pd/C as a catalyst and $PhSiH_3$ as a reductant. Next, the hydride transfer reaction occurs between phenyl silane and CO_2 led to the formation of intermediate C. The nucleophilic attack of A on the carbonyl group of intermediate C to delivered formamide intermediate D. Finally, benzimidazole (E) was obtained by cyclization followed by dehydration.

Recyclability

The recyclability of any catalyst is an important aspect to confirm the heterogeneous nature of catalysts (Fig. 2). For the recycle run, the 2-nitroaniline (0.5 mmol), $PhSiH_3$ (3 equi.), catalyst (10 mg, 0.01 mmol of Pd), TBD (5 mol %), CO_2 (1 MPa), ACN (7 mL), for 15 h at 70 °C. After completion of the reaction, the catalyst was recovered by centrifugation and used for the next recycled run. The Pd/C catalyst shows excellent performance, and it can be recycled up to five recycled runs without a noteworthy decrease in catalyst performance.

Conclusion

We have developed a simple and efficient route for the synthesis of benzimidazole from o-nitroaniline in the presence of Pd/C as a heterogeneous recyclable catalyst. A series of benzimidazoles were obtained in excellent to moderate yield relatively milder conditions. $PhSiH_3$ is used as an air and moisture stable hydrogen source compare to boranes. The synthesis of benzimidazole involves the hydrogenation of 2-nitroaniline to o-phenylenediamine, which further reacted with CO_2 to obtained formamide intermediate which undergo cyclization followed by dehydration to delivered benzimidazole. Furthermore, this catalyst can be recycled up to five recycled runs without a significant decrease in the yield of benzimidazole.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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