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ARTICLE

Mild and facile synthesis of Formamide: Reduction and functionalization of CO₂ using NaBH(OAc)₃ under atmospheric pressureReceived 00th January 20xx,
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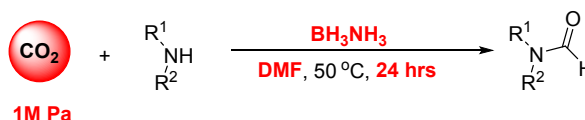
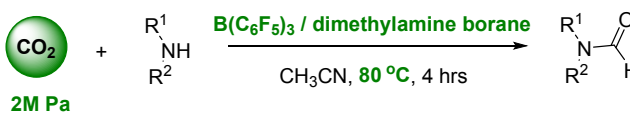
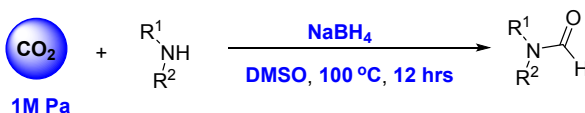
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An approach for N-formylation of amines was developed using NaBH(OAc)₃ as reductant under atmosphere pressure of CO₂ at 50 °C. The corresponding formylated products of various amines, including aliphatic and aromatic amines, amines with reductive-sensitive nitro groups and alkynyl groups as well as benzamide were obtained in good to excellent yields. And the possible reaction mechanism was also proposed.

The continuous accumulation of CO₂ as a greenhouse gas will lead to the global environmental problem. It is necessary to develop efficient routes for the conversion of CO₂. A promising transformation in this area is the reduction and functionalization of CO₂ with amines to produce formamides.^[1] As we all know, CO₂ is thermodynamically inert and stable, the conversion of CO₂ is yet challenging. The reported methods for the activation of CO₂ generally required expensive or complicated catalysts, such as Ru-pincer-type complexes,^[2] bis(tzNHC)-Rh complexes,^[3] [Ir(H)(CF₃SO₃)(NSiN)(coe)],^[4] Pd-Au bimetallic catalyst^[5] and organocatalysts.^[6-12] However, these catalysts were not capable of recyclability and generally accompanied with H₂ or hydrosilanes as reductants or high temperature and pressure.

Borohydride derivatives are known as hydrogen storage reagents with wide application in reduction reactions^[13-14] and also reported to be utilized in the reduction and functionalized of CO₂ with amines for the formation of formamides. For example, ammonia borane (BH₃NH₃) is reported as the reductant for the catalyst-free N-formylation of amines under 1M Pa pressure of CO₂. (Scheme 1a)^[15] And dimethylamine borane (Me₂NH·BH₃) was utilized as a hydrogen transfer source for the N-formylation of amines in the presence of organocatalyst B(C₆F₅)₃ under 2M pa pressure of CO₂. (Scheme 1b)^[16] Sodium borohydride (NaBH₄) was also employed to realize the N-formylation of amines under 1M Pa pressure of CO₂ in DMSO at 100 °C. (Scheme 1c)^[17] The transformation of

CO₂ to formamides *via* borohydride was proposed to proceed as follows. First, CO₂ reacts with borohydride to produce the boron-formate intermediate. Then, the nucleophilic N-atom of the amine attacks the above intermediate to generate the formamide products. Despite the successful delivery of formamides from various amines in the presence of borohydrides, these methods required high reaction temperature (100 °C), organocatalyst involvement or 1~2M pa pressure of CO₂. When the experiment was performed under 1 atmospheric pressure (~0.1 M pa) of CO₂, the desired formamide was obtained with a relatively low isolated yield of 5%.^[17] Therefore, it is highly needed to explore an efficient strategy for the conversion of CO₂ to formamides under atmospheric pressure of CO₂ at mild conditions.

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Scheme 1. Previous works on the N-formylation of amines with CO₂ using borohydride as reductants.

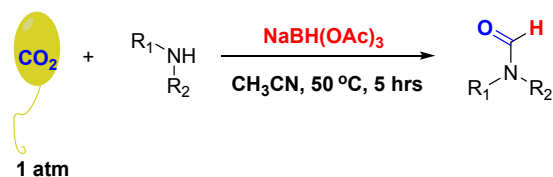
Sodium triacetoxyborohydride (NaBH(OAc)₃) is a mild hydrogen storage reagent that exhibits remarkable selectivity in

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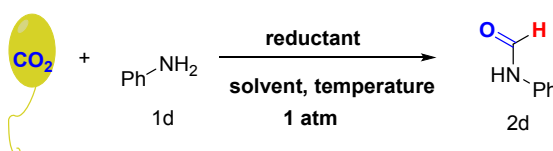
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reduction reaction. Additionally, compared to the boron-reducing agent NaBH_3CN , $\text{NaBH}(\text{OAc})_3$ is also an environmental reagent without the contamination of cyanide group.^[18] Moreover, the strong electron withdrawing effect of acetoxy groups of $\text{NaBH}(\text{OAc})_3$ may possibly attenuate the amines nucleophilic attack step in the functionalization of CO_2 . Herein, we report a reductive *N*-formylation of amines with CO_2 using $\text{NaBH}(\text{OAc})_3$ as a reductant, as illustrated in **Scheme 2**. It was demonstrated that $\text{NaBH}(\text{OAc})_3$ was efficient for the reaction in CH_3CN at 50 °C, and either aliphatic and aromatic amines or primary and secondary amines could be converted to the corresponding formamides in good to excellent yields under one atmospheric pressure of CO_2 .



Scheme 2. This work of a reduction and functionalization of CO_2 using $\text{NaBH}(\text{OAc})_3$ as reductant

Table 1. Optimization of reaction conditions



Entry	Solvent	Reductant	T (°C)	Conv. (%) ^a
1	1,2-dichloroethane	$\text{NaBH}(\text{OAc})_3$	50	89
2	DMSO	$\text{NaBH}(\text{OAc})_3$	50	90
3	DMF	$\text{NaBH}(\text{OAc})_3$	50	92
4	acetonitrile	$\text{NaBH}(\text{OAc})_3$	50	>99
5	THF	$\text{NaBH}(\text{OAc})_3$	50	70
6	CHCl_3	$\text{NaBH}(\text{OAc})_3$	50	59
7	toluene	$\text{NaBH}(\text{OAc})_3$	50	48
8	acetonitrile	$\text{NaBH}(\text{OAc})_3$	25	77
9	acetonitrile	$\text{NaBH}(\text{OAc})_3$	75	95

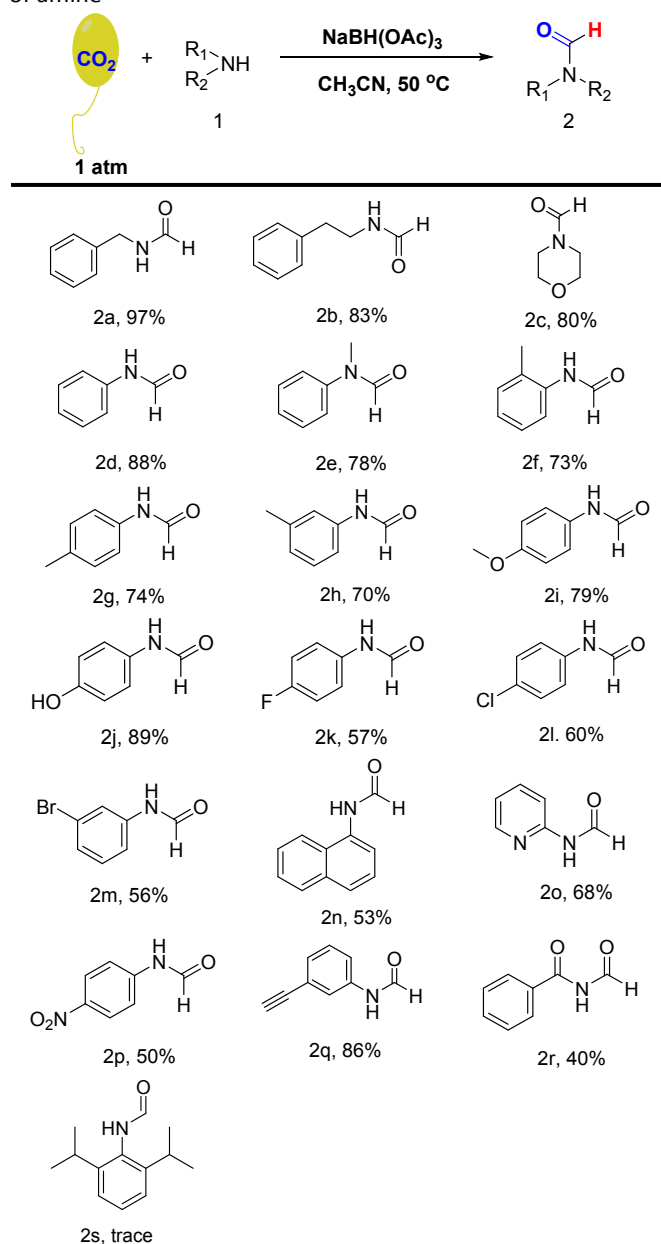
Reaction conditions: aniline (1 mmol), reductant (3 mmol), 6 mL of solvent, one atmospheric of CO_2 , 5 hrs. ^a Determined by high-performance liquid chromatography, through area normalization method.

In the initial optimization investigation, aniline **1d** was chosen as a model substrate using 3.0 equivalents of $\text{NaBH}(\text{OAc})_3$ as the reductant under 1 atmospheric pressure of CO_2 in 1,2-dichloroethane (DCE) at 50 °C. To our expectation, the desired *N*-formylation of aniline **2d** was obtained in a satisfied conversion of 89% (**Table 1**, entry 1). Encouraged by this, we further investigated the solvents used. When the DCE was replaced with CH_3CN , the conversion to **2d** can be improved to 99% (**Table 1**, entry 4). While, the alternation with THF, CHCl_3 , or toluene lead to lower conversions of 48-70% (**Table 1**, entries 5-7). However, we found that upon increasing the temperature to 75 °C or lowering to 25 °C would not improve the conversions

(**Table 1**, entries 8-9). Finally, the optimal reaction was efficiently proceeded with 3.0 equivalents of $\text{NaBH}(\text{OAc})_3$ as a reductant under one atmospheric pressure of CO_2 in CH_3CN at 50 °C.

With the optimized conditions in hand, a range of amines were investigated (**Table 2**). Aliphatic amines including benzylamine, phenethylamine and morpholine were successfully formylated giving the corresponding products **2a-2c** in good to excellent yields from 83-97%. Aromatic amines were also tolerant in this conditions. Aniline proceeded well to afford the desired **2d** in a yield of 88%.

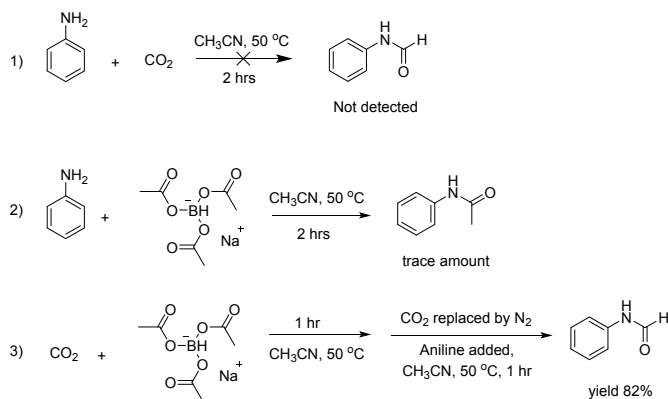
Table 2. The substrate scope investigation of the *N*-formylation of amine^a



^aReaction conditions: amine (1 mmol), $\text{NaBH}(\text{OAc})_3$ (3 mmol), acetonitrile (6 mL), one atmospheric CO_2 , 5 hrs. Isolated yields are given.

And the secondary aromatic amine, such as N-methylaniline, was also investigated and efficiently converted to **2e** with a comparable lower yield of 78%. Different substitution positions of methyl group on the benzene ring did not possess significant effect on the reaction with the similar isolated yields (**2f-2h**) of 73%, 74% and 70%, respectively. The electronic properties on the benzene ring were tested in this reaction. It is found that aniline with electron-donating groups such as OMe and OH afforded the corresponding formylated products **2i** and **2j** in 79% and 89% respectively. Halogenated substitutions (-F, -Cl, -Br) on aniline furnished the desired products **2k**, **2l** and **2m** in moderate yields. Aniline with strong electron-withdrawing group NO₂ could also be formylated, providing **2p** with an acceptable yield of 50%. Reductive-sensitive group alkynyl can be tolerated under this condition to deliver **2q** in good yield (86%). Additionally, benzamide was investigated for the substrate scope. To our delight, N-formylbenzamide (**2r**) was obtained in an acceptable yield of 40%. And the 2, 6-dimethylaniline afforded a trace of product **2s** possibly due to the high steric effect.

For a better understanding about this reaction, multiple control experiments have also been performed. As showed in **Scheme 3**, in the absence of NaBH(OAc)₃, the reaction failed to give the desired formamide. This indicated the important role of NaBH(OAc)₃. However, when the reaction performed without CO₂, only a trace amount of N-acetylated product could be detected after two-hour reaction. When CO₂ firstly reacted with NaBH(OAc)₃ for one hour, then the replacement of CO₂ with N₂ for another 60 minutes following the addition of one equivalent of aniline, the formylation reaction proceeded well with an isolated yield of 82%. Such results indicated CO₂ could be captured by NaBH(OAc)₃ forming an active intermediate that would further react with aniline to give the desirable product.

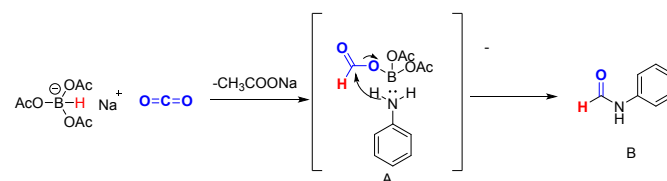


Scheme 3. Control experiments

According to the results above, a plausible mechanism of this reaction is proposed. (**Scheme 4**) First, CO₂ reacted with NaBH(OAc)₃ generating a boron-formate intermediate (**A**). Then amine nucleophilic attacked the intermediate (**A**) to afford the corresponding formamide product (**B**).

In conclusion, we have developed an N-formylation method under an atmospheric pressure of CO₂ at mild conditions (in CH₃CN, 50 °C, 5 hours). Using NaBH(OAc)₃ as reductant, this transformation was proceeded well with a good tolerance of

various substrates, including aliphatic and aromatic amines, amines with reductive-sensitive nitro groups and alkynyl groups as well as benzamide in good to excellent yields. Control experiments were also studied and a plausible mechanism was proposed.



Scheme 4. Proposed mechanism of N-formylation with NaBH(OAc)₃ and CO₂

Conflicts of interest

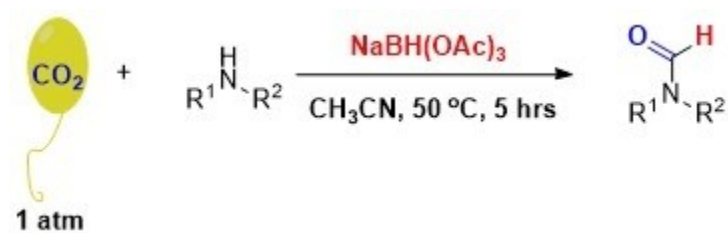
There are no conflicts to declare.

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