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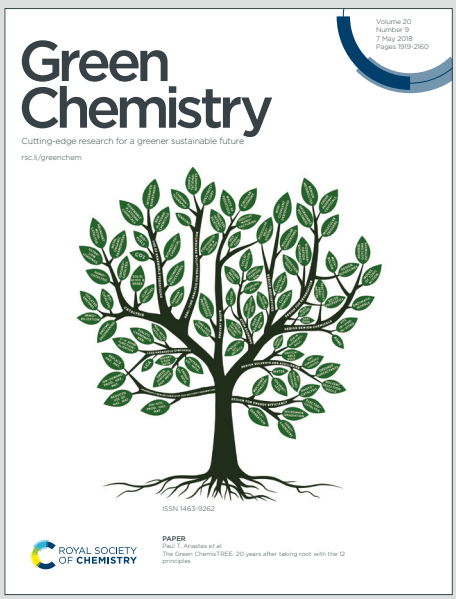

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DOI: 10.1039/C9GC03637G

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COMMUNICATION

Catalyst-free selective *N*-formylation and *N*-methylation of amines using CO_2 as a sustainable C1 source‡

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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We herein describe a catalyst-free selective N-formylation and N-methylation of amines using CO_2 as a sustainable C1 source. By tuning reaction solvent and temperature, the selective synthesis of formamides and methylamines is achieved in good to excellent yields using sodium borohydride ($NaBH_4$) as a sustainable reductant.

CO_2, as an abundant and green sustainable C_1 feedstock, is used widely to build value added chemicals.[1] Especially, synthesis of formamides and methylamines by reductive functionalization of CO_2 is very attractive in recent years.[2] However, this process is challenging because CO_2 molecules are highly stable. Therefore, the boranes[2a-c] and hydrosilanes[2d-h] are used as highly active reductants in above processes. Even so, many processes still require metal or non-metal catalysts, especially when hydrogen is used as a reductant.[3] For all we know, metal catalysts with remarkable activity, such as Ru,[3a] Rh,[3b] Pd,[3c] Cu,[3d] Zn,[3e] and Fe[3f], have been reported.[3] In contrast, a number of organocatalysts, involving superbases,[4a] *N*-heterocyclic carbenes (NHCs),[4b,c] $B(C_6F_5)_3$,[4d] and ionic liquids (ILs)[4e] have also revealed moderate activity.[4]

Although above results are encouraging,[3,4] most of these processes still require high temperature and pressure (H_2 as reductant), and low atomic economy (hydrosilanes as reductants). Otherwise, how to control the chemoselectivity of reduction products is also essential.[5] Many pioneering works in this area have achieved great results. In 2016, Fu et al.[5a] established Cs_2CO_3 system to display remarkable reactivity for the selective *N*-formylation and *N*-methylation using CO_2 and hydrosilanes. Whereafter, a hierarchical reduction of CO_2 with amine and diphenylsilane (Ph_2SiH_2) was acquired by using glycine betaine as a catalyst.[5b,c] Recently, Xia et al.[5d] reported DBU-catalyzed selective *N*-formylation and *N*-methylation of amines with CO_2 and polymethylhydrosiloxane (PMHS). Almost simultaneously, He and coworkers developed a pressure-switched and K_2WO_4-catalyzed as a catalyst strategy for selective *N*-formylation and *N*-methylation of amines using CO_2 and phenylsilane ($PhSiH_3$).[5e] The above processes usually use hydrosilanes as the reductants, but the inherent disadvantages of using hydrosilanes will result in relatively low atomic economy. And the recovery of the catalyst is also difficult. In addition, for some catalyst-free examples, selective *N*-formylation and *N*-methylation of amines have not been achieved concurrently using the same reducing agent.[6] Hence, the development of the catalyst-free and high atom efficient methodology is essential for CO_2 fixation to formamides and methylamines in a perspective of green chemistry.

The metal borohydrides are inexpensive reductants, which can react with CO_2 to form formate borohydride species.[7] By comparison, a more attractive strategy is replacing hydrosilanes with the inexpensive metal borohydrides. In this respect, several examples reveal the feasibility of CO_2 reduction functionalization using $NaBH_4$ and $NaBH(OAc)_3$.[8] In our previous work, we developed a catalyst-free *N*-formylation of amines using CO_2 and NH_3BH_3,[9] however, the reaction does not selectively obtain methylated products, and the expensive price of NH_3BH_3 is not conducive to large-scale synthesis.

Inspired by above results, we want to realize here a catalyst-free selective *N*-formylation and *N*-methylation of amines using CO_2 and inexpensive metal borohydrides. In the course of our study on the conversion of CO_2, we unexpectedly discovered that formamide and methylamine can be produced simultaneously by using $NaBH_4$ as reductant. The reaction solvent and temperature can significantly affect the selectivity of the product. So we performed initially the reaction in various solvents using *N*-methylaniline (**1a**) as a model

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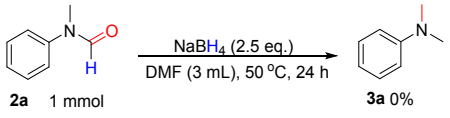
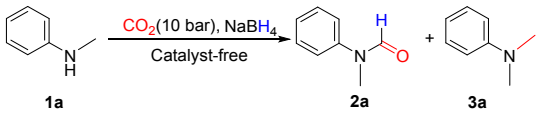
‡*Electronic supplementary information (ESI) available: Details on synthesis* of formamides and methylamines, mechanism research, and NMR information of formamides and methylamines.

substrate at 50°C to investigate the selective *N*-formylation and *N*-methylation (See SEI ‡). To our delight, the best result with a 94% yield of **2a** was obtained in DMF (Table 1, Entry 1), suggesting that solvent can activate the N-H bond of **1a** through polarization and solvation.[6,10] Both KBH_4 and $NaBH(OAc)_3$ are also effective for *N*-formylation, affording **2a** in 91% and 89% yield (Entry 2 and 3), respectively. Next we tried to enhance the selectivity of the methylated product. Before this, some previous works[11] supported further reduction of formamide to form methylamine. Thus, we are just trying to increase the amount of $NaBH_4$ to get more methylation products. However, only 18% yield of **3a** was obtained by using 4 eq. of $NaBH_4$ (Entry 11). To further clarify the mechanism, **2a** was also tested to react with the $NaBH_4$ (**Eq.1**). The result showed that the reaction cannot take place meaning that formamide was unlikely to be the intermediate for the *N*-methylation.



(Eq. 1)

Table 1 Optimization of reaction conditions.

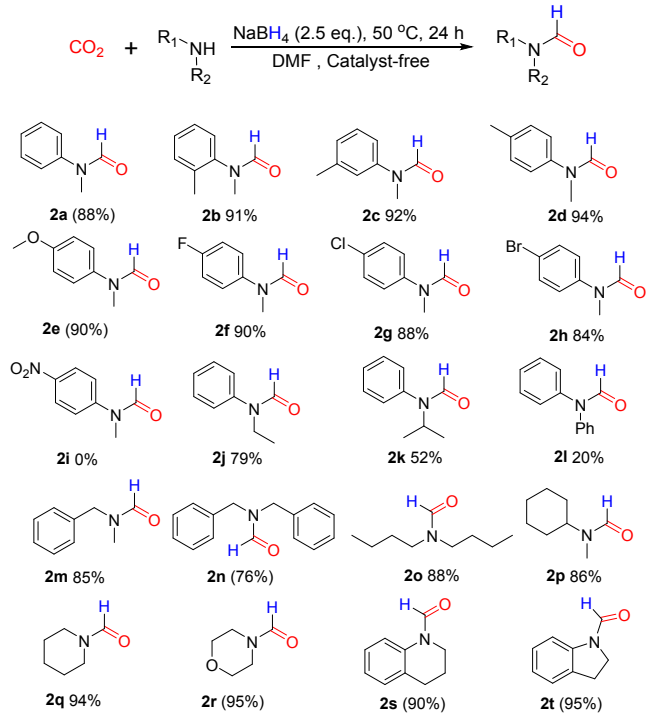


Entry	Solvent	*T* (°C)	$NaBH_4$ (mmol)	Yield of **2a** (%)[a]	Yield of **3a** (%)[a]
1	DMF	50	2.5	94	6
2[b]	DMF	50	2.5	91	7
3[c]	DMF	50	2.5	89	10
4	DMF	50	4	82	18
5	DMF	50	1	61	Trace
6[d]	DMF	50	2.5	77	12
7[e]	DMF	50	2.5	42	Trace
8[f]	DMF	50	2.5	0	0
9	DMF	100	4.0	87	13
10	CH_3CN	100	4.0	33	57
11	THF	100	4.0	25	66
12	1,4-dioxane	100	4.0	11	85
13[e]	1,4-dioxane	100	4.0	10	72
14	1,4-dioxane	100	2.5	6	55

Reaction conditions: amine **1a** (1.0 mmol), solvent (3 mL), CO_2 (10 bar), reaction time (24 h). [a]The yields were determined by GC/MS using dodecane as the internal standard. [b]2.5 mmol of KBH_4. [c]2.5 mmol of $NaBH(OAc)_3$. [d]Reaction time 12 h. [e]CO_2 (1 bar). [f]CO_2-free.

Reducing the amount of $NaBH_4$ and reaction time led to a decrease in yield of **2a** (Entry 5 and 6). The pressure of CO_2 also affected the yield of **2a**. Specifically, the yield of **2a** decreased to 42% at 1 bar of CO_2 (Entry 7). In contrast, at higher pressure of 10 bar of CO_2, more CO_2 can be dissolved in the liquid phase to react with $NaBH_4$ and amine, resulting in higher yield of **2a** (Entry 1 vs Entry 7). In addition, to exclude the possibility of DMF participating in the reaction, the reaction was performed in the absence of CO_2, and no product was detected (Entry 8). Noteworthy, when the reaction was carried out in 1,4-dioxane under the same conditions, the methylated product **3a** was obtained in 33% yield (Table S1, Entry 6). The yield of **3a** increased observably to 85% (Entry 12) with increasing reaction temperature along with **2a** in a 11% yield, while poor selectivity of **3a** was observed in DMF, CH_3CN, or THF under same conditions (Entry 9-11), indicating that the solvent and reaction temperature played the critical role in the selectivity and reactivity. Shortening reaction time or decreasing $NaBH_4$ led to reduction of **3a** yield (Entry 13 and 14).

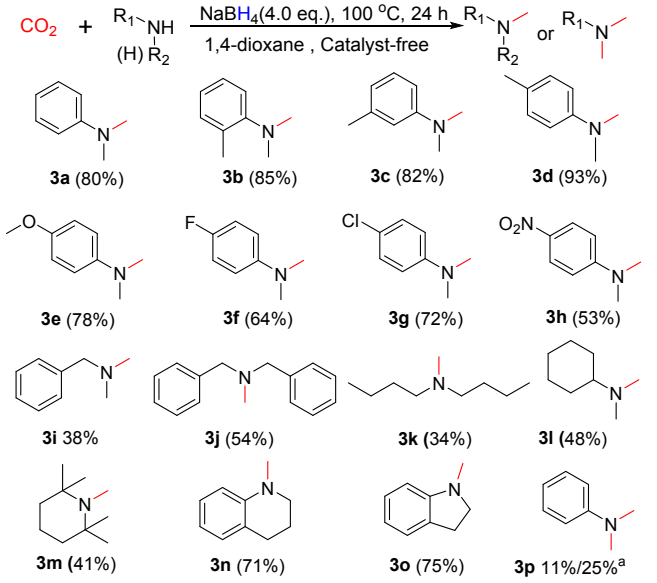
With the optimized reaction conditions in hand, the substrate scope of *N*-formylation with various amines (Scheme 1) was evaluated firstly. We found that both aromatic and aliphatic secondary amines converted into the desired formamides in excellent yields. For instance, **2a** was achieved in an isolate yield of 88%. Most of the *N*-methylanilines with both electron-withdrawing and electron-donating groups in the phenyl ring were well tolerated (**2b**-**2h**), giving the yields of up to 94%. Interestingly, the electronic property of the functional group on the amines affected observably the reaction activity. The substrate of *N*-methyl-4-nitroaniline was unreactive (**2i**) because a strong electron-withdrawing effect that weakens greatly the nucleophilicity of the amine. The *N*-alkyl substituent on the secondary monoaromatic amines led to the declining yields (**2j**-**l**), presumably because of the steric hindrance. The aliphatic amines also converted to the corresponding formamides in moderate yields (**2m**-**p**). In addition, this protocol could expand to several heterocyclic amines (**2q**-**t**), affording the yields of up to 95%. However, only the trace of the product was detected using aniline as reactant, presumably because weak nucleophilic aniline cannot trap the weak electrophilic formate intermediate.[12]



Scheme 1 Substrate scope of the *N*-formylation. Reaction conditions: amine (1.0 mmol), CO_2 (10 bar), and DMF (3 mL). The yields were determined by the ^1H NMR using 1,3,5-trimethyoxybenzene as an internal standard. Isolated yields are given in parentheses.

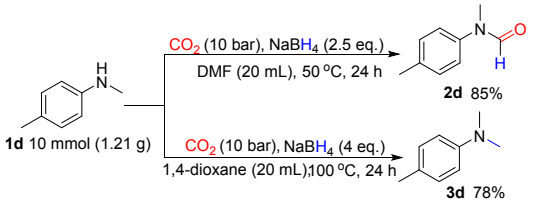
We evaluated subsequently substrate scope of the *N*-methylation of amines by tuning the reaction temperature and solvent. The

summary of results is presented in Scheme 2. We found that the secondary monoaromatic amines, both electron-withdrawing and electron-donating group on the aromatic ring, could be methylated, affording the corresponding methylamines in 64-93% yields (**3a**-**g**). The weak nucleophilicity *N*-methyl-4-nitroaniline is relatively inert, giving the desired **3h** in a 53% yield. Some representative aliphatic amines were further investigated, but they showed lower selectivity for the corresponding methylated products (**3i**-**3m**), preferring the formation of formylation products. Particularly, this protocol could be also applicable to heterocyclic amines, such as 2,3-dihydro-1H-indole (**1n**) and 1,2,3,4-tetrahydroquinoline (**2n**) to afford the corresponding products in 71% (**3n**) and 75% (**3o**) yield, respectively. In addition, the *N*-methylation was carried out using aniline as the substrate under the above optimized conditions (See SEI‡), but dimethylated product was only obtained in 11% yield (**3p**). The yield of **3p** could be increased to 25% by lengthening of reaction time, indicating that the aniline was also compatible with the optimized conditions, despite low reactivity of the aniline.



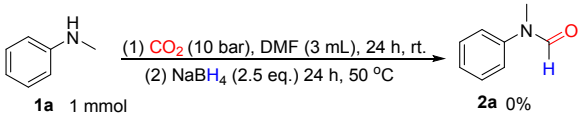
Scheme 2 Substrate scope of the *N*-methylation. Reaction conditions: amine (1.0 mmol), CO_2 (10 bar), and 1,4-dioxane (3 mL). The yields were determined by the ^{1}H NMR using 1,3,5-trimethyoxybenzene as an internal standard. Isolated yields are given in parentheses. [a] Reaction time (48 h).

To verify the applicability of the present methodology, the reactions of the *N*-formylation and *N*-methylation were performed on the gram scale (**Eq. 2**). The desired products **2d** and **3d** were achieved in 85% and 78% isolated yields, respectively. It suggests that this catalyst-free and efficient methodology has a potential application for large-scale synthetic chemistry.

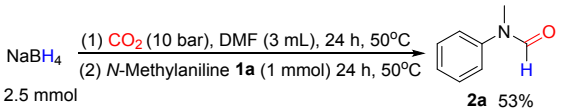


(Eq. 2)

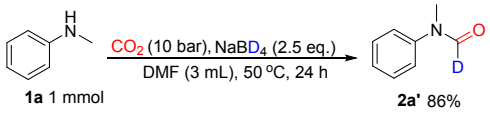
To study the mechanism of the reaction, several control experiments were designed respectively under the standard conditions. Considering that CO_2 can react with primary or secondary to produce carbamates,[9a] and CO_2 and amine-CO_2 adduct coexist in equilibrium,[9b] reducing CO_2 and CO_2-amine adduct with $NaBH_4$ were carried out separately. The experimental results indicated that reaction did not undergo amine-CO_2 adduct intermediate pathway in our study (**Eq. 3**). Similar result was also obtained by reducing morpholine (**1r**) carbamate, thereby further confirming that carbamates is not an intermediate in the reaction (See SEI‡). Whereafter, we designed a stepwise reaction of $NaBH_4$, CO_2 and **1a** (**Eq. 4**). It is interesting to find that the formate borohydride species [$NaH_{4-n}B(OCOH)_n$] was formed preferentially during the reduction of CO_2 with $NaBH_4$ in DMF, which was confirmed by NMR (Fig. S1) and defined to **Int.1** (Scheme 3).[7] Especially, it can further react with **1a** to produce **2a** in a 53% yield. The result suggested that **Int.1** was a key intermediate in the formylation reaction of **1a** and CO_2 using $NaBH_4$ as the reductant. Indeed, if $NaBH_4$ was instead with $NaBD_4$ in the reaction of **1a** and CO_2, the containing deuterium **2a** was obtained in a yield of 86% (**Eq. 5**), supported by NMR analysis (Fig. S2), further proving that $NaBH_4$ acted as the reductant in the formylation reaction of amine and CO_2.



(Eq. 3)

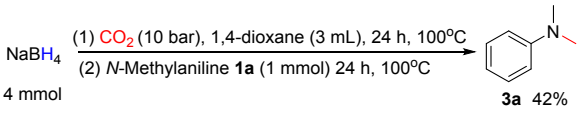


(Eq. 4)

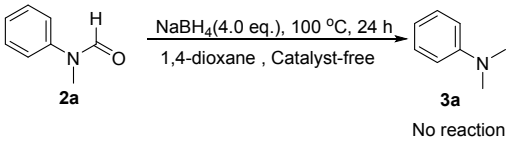


(Eq. 5)

Analogously, to insight into the reaction mechanism of methylation, the reaction of CO_2 with $NaBH_4$ was performed in 1,4-dioxane for 24 h at 100°C. The results of the ^{1}H NMR and ^{13}C NMR suggested that the CO_2 was reduced to the **Int.2** (Fig. S3), and then **3a** was detected in a yield of 42% when equimolar **1a** was added into the reaction solution of CO_2 and $NaBH_4$ at 100°C (**Eq. 6**), meaning that **Int.2** was the key intermediate of methylation. Accordingly, the ^{11}B{H} NMR spectrum signals at 19.5 and 1.4 ppm also implied generation of **Int.2** as major and **Int.1** as minor.[13] In addition, we performed a control experiment using $NaBH_4$ to reduce **2a** under the harsher N-methylation optimized conditions (**Eq. 7**). The result shows that the reaction cannot occur, implying that formamide was not an intermediate for the synthesis of methylamine.

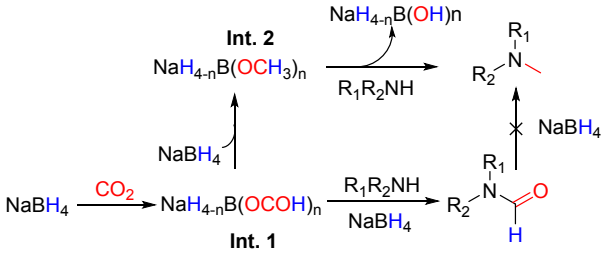


(Eq. 6)



(Eq. 7)

Based on the experimental results and previous reports,[3-7] a possible reaction mechanism is proposed (Scheme 3). Firstly, CO_2 reacts with $NaBH_4$ in DMF to produce the **Int.1**. Then, amine as a nucleophilic reagent attacks the carbon atom of intermediate **Int.1** to form the *N*-formylation product. For *N*-methylation process, CO_2 reacts with $NaBH_4$ in 1,4-dioxane to produce **Int.1,** followed by further reaction with $NaBH_4$ affords intermediate **Int.2**. Finally, the nucleophilic reagent of amine attacks the carbon atom of intermediate **Int.2** to form the *N*-methylated product. In fact, the effect of solvent is still not clear in above processes, we speculated that both DMF and 1,4-dioxane coordinated to sodium ion,[7a,14] making the insertion of CO_2 much easier to form the intermediate, and led to the reaction with selectivity to afford desired formamides and methylamines.



Scheme 3 The possible mechanism of formylation and methylation of amine using CO_2 and $NaBH_4$.

Conclusions

In conclusion, we have developed a catalyst-free and efficient selective *N*-methylation and *N*-formylation of amines for the synthesis of formaides and methylamines with CO_2 as a sustainable C_1 source and inexpensive $NaBH_4$ as a reductant. By tuning solvent and reaction temperature, both selective *N*-methylation and *N*-formylation of amines can be controlled smoothly, affording desired products of formaides and methylamines in good yields.

Acknowledgement

This work was supported by Natural Science Special Foundation of Guizhou University (No. X2019065 Special Post A) and Scientific and Technological Innovation Talents Team Project of Guizhou Province (NO.20185607).

Conflicts of interest statement

We have no conflicts of interest to declare.

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View Article Online
DOI: 10.1039/C9GC03637G

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