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1,4-Dioxane-tuned Catalyst-free Methylation of Amines using CO_2 and $NaBH_4$

Zhiqiang Guo,[a,b] Bo Zhang,[b] Xuehong Wei,[a] and Chanjuan Xi*[b]

Abstract: A catalyst-free reductive functionalization of CO_2 with amines and $NaBH_4$ was achieved. This protocol realized the *N*-methylation of amines using CO_2 as a C1-building block in the 1,4-dioxane as solvent. Notably, the six-electron reduction of CO_2 to the methyl with formation of C-N bond was attained simultaneously.

Methylamines are important chemicals and core structures existing in medicines, natural products, dyes, etc.[1] Conventionally, methylamines were prepared by using formaldehyde and hazardous methylating reagents including methyliodide, dimethylsulfate or dimethylcarbonate.[2] So a green and sustainable methodology for methylamines is desired, and the reduction of CO_2 to methylamines is an alternative and promising method for recycling CO_2 to value-added chemicals due to CO_2 is an attractive, inexpensive, nontoxic and abundant carbon source. Especially, reductive functionalization of CO_2 with amines provided a straightforward method for construction of carbon-nitrogen bond.[3]

Beller's group [4] and Cantat's[5] reported Ru and Zn catalyst system for conversion of CO_2 and amines into various kinds of *N*-methylated products in the presence of hydrosilanes in 2013, respectively. The methylation of amines *via* six-electron reduction of CO_2 have been attracted an attention. Many types of catalysts have been developed to reduce functionalization of CO_2 for methylamines using different reductants. For example, metal-based catalytic systems including alkaline metal such as cesium,[6] inexpensive transition metals (Fe,[7] Cu,[8] Zn,[5] Ni,[9]), and noble metals (Ru,[4, 10] Pd,[11] Pt,[12] Au[13]), as well as organic and inorganic molecule catalysts, such as *N*-heterocyclic carbenes,[14] carbodicarbene,[15] proazaphosphatrane superbases,[16] $B(C_6F_5)_3$,[17] TBAF (tetrabutylammonium fluoride),[18] glycine betaine,[19] carboxylate,[6] tungstate[20] and so on. It is noteworthy that He's group has achieved the hierarchical reduction of CO_2 with amine and hydrosilane to selectively access formamides, aminals, and methylamines using glycine betaine as catalyst.[19a] More recently, Lei and coworkers realized the catalyst-free methylation reactions of amines with CO_2 in the presence of phenylsilane.[21] All mentioned studies adopted dihydrogen and hydrosilanes as reducing reagents. Sodium borohydride ($NaBH_4$), an inexpensive, ease to handle, and mild reductant, has been rarely reported for the conversion of CO_2 and amines into *N*-methylated products, although a reductive formylation of amines with CO_2 using $NaBH_4$ as a reductant has been reported by Liu and coworkers.[23] Herein, we report a catalyst-free highly selective methylation of amines using CO_2 and $NaBH_4$. This protocol realized the six-electron reduction of CO_2 to the methyl with the formation of the C-N bond.

The initial optimization studies were explored using *N*-methylaniline (**1a,** 0.5 mmol) as a model substrate. The results are listed in Table 1. First, the reaction was treated in 1,4-dioxane solution at atmospheric pressure of CO_2 using two equivalents of $NaBH_4$ as reductant at 100 °C within 24 h, and methylated product, *N,N*-dimethylaniline (**2a**) was obtained in 36% yield along with trace amount of *N*-methylformanilide (**3a**) (entry 1). To improve the yield, increasing the CO_2 pressure to 1 MPa, the yield of **2a** increased to 71% while the **3a** was also obtained in 23% yield (entry 2), the selectivity was significantly reduced. This maybe owing to high CO_2 pressure representing high CO_2 concentration and a large excess of CO_2 would consume $NaBH_4$. When increasing the amount of $NaBH_4$, the yield and selectivity of **2a** increased obviously (entry 3-5), which suggested that the ratio of CO_2 and $NaBH_4$ affects selectivity. Subsequent methylation of **1a** with three equivalents of $NaBH_4$ afforded the desired product **2a** in nearly quantitative yield (98%, entry 4). Then, different solvents such as dichloroethane (DCE), tetrahydrofuran (THF), acetonitrile, ethanol, toluene, dimethyl sulfoxide (DMSO) and solvent-free were screened (entry 6-12), and poor yield and low selectivity were observed, which indicated that the solvent also play a critical role on the selectivity and reactivity of the reaction. The 1,4-dioxane is a best solvent for this reaction. Then, a mixture of solvent such as different ratio of dioxane and toluene was conducted in this protocol (see SI-Table 1 in supporting information). The results indicated with increasing of amount of dioxane, the methylated product increased. Furthermore, the effect of reaction temperature was also examined (entries 13-14), the best temperature for getting approving yield was 100 °C (entry 4). In addition, we tried to shorten the reaction time, the yield of **2a** also decreased (entry 15), notably, the yield over than 90% can still be obtained.

With the optimized reaction conditions in hand, the scope of this methylation with various amines was investigated. The representative results are summarized in Scheme 1. The *para*-substituted *N*-methylanilines with either electron withdrawing or electron donating groups were tolerated, and the corresponding *N,N*-dimethylanilines were obtained over 90% yields (**2b**-**2e, 2f** and **2l**). With stronger electron withdrawing group aniline such as *N*-methyl-4-(methylformate)aniline, *N*-methyl-4-cyanoaniline, and *N*-methyl-4-nitroaniline, are relatively inert, only giving the desired

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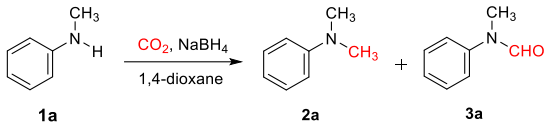
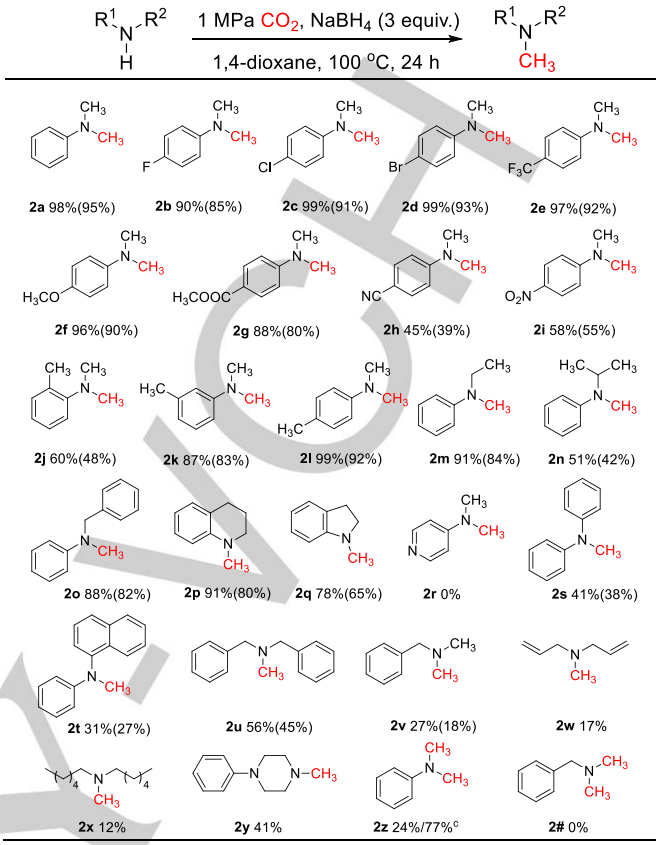
Table 1. Optimization for the selectively reductive functionalization of CO_2 with N-methylaniline[a]



Entry	$NaBH_4$ (mmol)	Solvent	2a (%)[b]	3a (%)[b]
1[c]	1.0	1,4-Dioxane	36	<1
2	1.0	1,4-Dioxane	71	23
3	1.25	1,4-Dioxane	90	9
4	1.5	1,4-Dioxane	98(95)	_
5	1.75	1,4-Dioxane	97	_
6	1.5	THF	66	23
7	1.5	Acetonitrile	52	38
8	1.5	Ethanol	_	_
9	1.5	DMSO	23	50
10	1.5	Toluene	42	26
11	1.5	DCE	34	43
12	1.5	-	29	10
13[d]	1.5	1,4-Dioxane	70	8
14[e]	1.5	1,4-Dioxane	97	<1
15[f]	1.5	1,4-Dioxane	90	<1

[a] Reaction conditions: *N*-methylaniline (54 μL, 0.5 mmol), $NaBH_4$, 1 MPa CO_2, 1,4-dioxane (0.5 mL), 100 °C, 24 h. [b] Yield determined by ^1H NMR using trichloroethylene as an internal standard, isolated yield is given in parentheses. [c] 1 atm, [d] 90 °C, [e] 110 °C, [f] 18 h.



Scheme 1. Substrate scope for *N*-methylation[a]. [a] Reaction conditions: amines (0.5 mmol), $NaBH_4$ (1.5 mmol), CO_2 1 MPa, 1,4-dioxane (0.5 mL), 24 h. [b] Yield determined by 1H NMR using trichloroethylene as an internal standard, isolated yields were given in parentheses. [c] Anline (0.5 mmol), $NaBH_4$ (3 mmol), CO_2 1 MPa, 1,4-dioxane (0.5 mL), 120 °C, 24 h.

product **2g, 2h,** and **2i** in 88%, 45%, and 58% yield, respectively, because of weak nucleophilicity. Furthermore, *ortho*-, *meta*-, and *para*- substituent were also well tolerated and the corresponding products (**2j**-**2l**) were obtained in 99%, 87%, and 60% yield, respectively. Notably, the substituent in the *ortho* position led to decreased yield of the target product, presumably due to steric hindrance. *N*-Alkyl anilines, such as ethyl, isopropyl, and benzyl were also used as substrates, the methylated products were obtained in 51-91% yield (**2m**-**2o**). Additionally, this protocol could apply to heterocyclic amines, such as 1,2,3,4-tetrahydroquinoline and 2,3-dihydro-1*H*-indole to afford the corresponding products (**2p**-**2q**) in 91% and 78% yield, respectively. When *N*-methylpyridin-4-amine was employed in this reaction and desired product **2r** was not observed. The reactivity of diarylamines is suppressed perhaps owing to the dual effects of steric hindrance and electronic effect, and the expected reactions occurred with lower yields of the methylated products (**2s**-**2t**). We also chose some representative aliphatic amines for screen. They showed lower selectivity for their corresponding methylated products (**2u**-**2y**) while the formylated products were obtained, probably because of the stronger nucleophilicity.

Next, the primary amines were also considered. The methylated reaction was carried out using aniline as the substrate under the above optimized condition, and the dimethylated product (**2z**) was obtained in 24% with some amount of *N*-methyl-formanilide. Although the selectivity and activity of initial reaction were relatively lower, the primary aromatic amine was also compatible with the reaction conditions. And dimethylated product was obtained dominantly by elevating temperature to 120 °C and increasing the amount of $NaBH_4$, albeit the yield of dimethylated product was only 77%. In addition, no dimethylated product (**2#**) was observed when benzylamine using as a substrate in the reaction.

To verify the applicability of current methodology, the reaction was amplified to 10 mmol scale (gram scale) with a yield of *N*-methylated product at 84% (1.02 g) using 3 equiv. of $NaBH_4$ in 10 mL of 1,4-dioxane (Eq 1).

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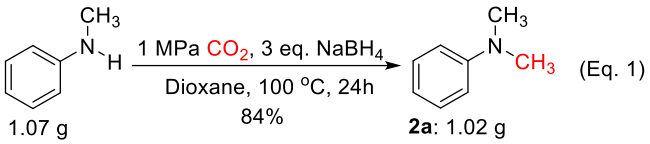
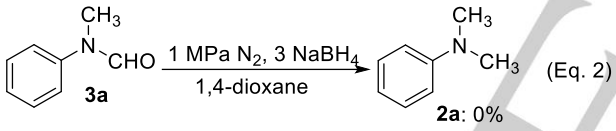
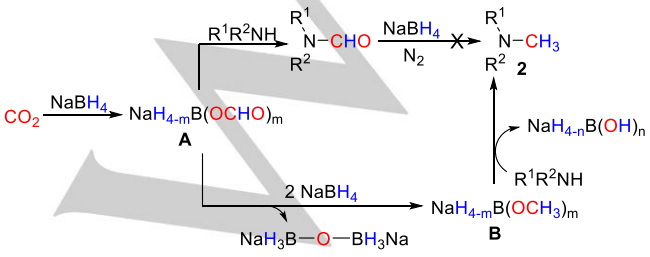


Inspired by this interesting discovery and achieving a better understanding of the reaction process, further ^{1}H NMR, ^{13}C NMR and ^{11}B NMR spectroscopy were exploited (NMR spectrum see supporting information). The reaction of CO_2 with $NaBH_4$ was performed in 1,4-dioxane-d^8 for 24 h at 100 °C under 1 MPa. In the ^{1}H NMR spectrum, the signals around 3.75-3.37 ppm were obtained as major, which indicated that the CO_2 was reduced to the boron methoxide B-$(OCH_3)_m$. Meanwhile the signals 8.10-8.00 ppm were also observed as trace, which assigned to B-$(OCHO)_m$. Additionally, the signals at 51, 50 ppm were observed in the ^{13}C NMR spectrum, which also indicated the formed of -$(OCH_3)_m$ in this reaction, and the signals at 162 and 125 ppm were also observed, which corresponded to -$(OCHO)_m$. Accordingly, there were also signals at 18.1, 17.5, and 0.58 ppm in the corresponding ^{11}B NMR spectrum. All these signals and the corresponding peaks indicated that the generation of $NaH_{4-m}B(OCH_3)_m$ as major and $NaH_{4-m}B(OCHO)_m$ as trace.

To further understand the mechanism of this reaction, we tried the reaction of *N*-methyl-*N*-phenylformamide (**3a**) with $NaBH_4$ under N_2 atmosphere (Eq. 2), the methylation product (**2a**) was not observed. This result indicated that *N*-methyl-*N*-phenylformamide (**3a**) was unlikely to be the intermediate for methylation product.



Based on the above experimental results and previous reports[23] on the reductive functionalization of CO_2 with $NaBH_4$, a possible reaction mechanism is proposed as shown in Scheme 2. First, CO_2 reacts with $NaBH_4$ in 1,4-dioxane to produce the formatoborohydride intermediate (**A**). Then, further reduction of the intermediate (**A**) with 2 equiv. of $NaBH_4$ affords methoxyboroxine intermediate (**B**), Finally, the amine as a nucleophilic reagent attacks the carbon atom of intermediate (**B**) to form the desired *N*-methylated product **2**. In addition, although the factor of 1,4-dioxane as solvent is not clear, in this process, 1,4-dioxane maybe coordinated to sodium ion,[23] which made the $[H_{4-m}B(OCHO)_m]^-$ more reactive and led to the reaction with selectivity to afford the *N*-methylated product **2**.



Scheme 2. Possible mechanism of *N*-methylated reaction with CO_2.

In summary, we reported a 1,4-dioxane tuned catalyst-free and selective 6-electron reductive functionalization of CO_2 by $NaBH_4$ for the highly selective methylation of N-H bond. In this system, a variety of amines could be turned into the desired *N*-methylated products in moderate to excellent yields. Further detailed studies on this selective reductive mechanism and to expand the utility of this system are in progress in our group.

Experimental Section

General procedure for the reductive functionalization of CO_2 with amines to methylamines

Sodium borohydride (56.7 mg, 1.5 mmol), amine (0.5 mmol), 1,4-dioxane (0.5 mL) were added successively into a 25 mL (inner volumes) stainless steel autoclave coupled with a magnetic stirrer at room temperature. Then CO_2 was charged into a reactor up to 1 MPa. The autoclave was heated at 100 °C for 24 h. Upon completion, the reactor was cooled to room temperature and carefully depressurized to atmospheric pressure. The residue was carefully quenched with water and the mixture was extracted with ethyl acetate. The yields were determined by ^{1}H NMR technique using trichloroethylene (45 μL, 0.5 mmol) as an internal standard. The reaction mixture was purified by neutral alumina column chromatography with petroleum ether/ethyl acetate as the eluent to afford the desired methylamines. All of the products were characterized by NMR techniques.

Acknowledgements

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Keywords: Carbon dioxide • Sodium borohydride • Reduction • *N*-methylation • Catalyst-free

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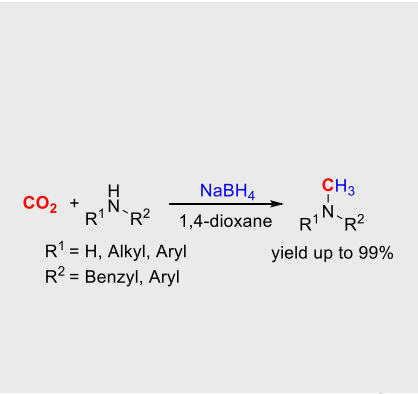

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