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Catalyst-free *N*-Methylation of Amines Using CO_2

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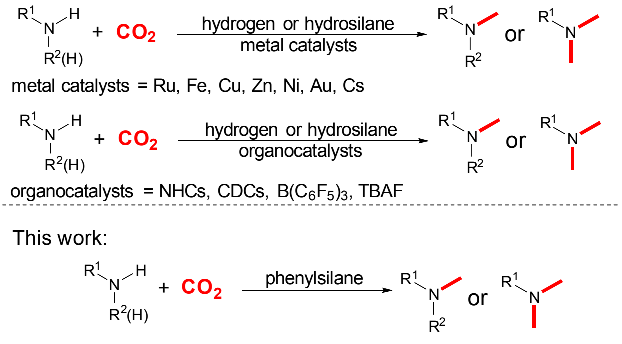
Recently, utilizing CO_2 as a methylation reagent to construct functional chemicals has attracted much more attention. However, the conversion of CO_2 is still a challenge due to its inherent inertness. In this work, we developed a catalyst-free methylation of amines to prepare numerous methylamines, using CO_2 as methyl source. By utilizing the 2 eq. $PhSiH_3$ as the reductant, amines could be proceeded methylation under 1 atm CO_2 in DMF at 90 °C. Aliphatic and aromatic amines were compatible, generating the desired products in up to 95 % yield.

On the earth, most of the carbon exists in the form of carbon dioxide and carbonates. Nowadays, excess consumption of fossil fuels leads to the increasing concentration of CO_2 in the air, which aggravates greenhouse effect. Hence transforming CO_2 into fuels and valuable chemicals is an ideal way to fix this greenhouse gas.[1] Although CO_2 is an economic and nontoxic C1 building block, the way of CO_2 activation is still less due to its thermodynamic stability and kinetic inert, which calls for a large driving force.[2] Up to now, most of the previous works on CO_2 conversion suffer from highly reactive substrates or harsh conditions, such as high pressure and temperature, limiting the applications of these methods.[3]

Therefore, develop more applications in CO_2 activation is very important. Recently, the investigations of the inert CO_2 molecule converted with amines to generate formamide, formamidine and methylamine derivatives by different reductants have been reported.[4] Moreover, it's worth noting that the methyl-substituted amines represent core structures in drugs, natural products, dyes, etc.[5] In 2013, Beller et al.[6] and Cantat et al.[7] developed Ru- and Zn-catalyzed system converting CO_2 and amines into various kinds of *N*-methylated products in the presence of hydrosilanes. Subsequently, Cantat and co-workers reported the first metal-free methylation of amines by using phosphorus base as catalyst.[8] In recent years, methylation of amines with CO_2 based on metal catalysts[6, 9-13] and organocatalysts[8, 14-16] have been developed as shown in Scheme 1. Herein, we report a catalyst-free methylation of amines using CO_2 under mild conditions. This protocol realized the reduction of CO_2 and coupled C–N bond without catalysts, providing a simple and new way to perform the methylation reactions on several amines.



Scheme 1 Previous works on methylation of amines

In the initial optimization investigations, we employed *N*-methylaniline (**1a**) as model substrate, with 2 eq. of Ph_2SiH_2 as reductant under 1 atm CO_2 in DMF at 90 °C, the desired product **2a** can be obtained in 54% yield (Table 1, entry 1). Notably, we found that when Ph_2SiH_2 was replaced to $PhSiH_3$, the generation of **2a** can be improved to 81% yield (entry 2). However, we found that treatment of 1 eq. $PhSiH_3$ will decrease the yield to 41% (entry 3), it means that $PhSiH_3$ would be needed more than 1 eq. to complete the reaction under whole process. In the control experiments, without CO_2 or $PhSiH_3$, the reaction could not be performed (entries 4 and 5). With this encouraged, solvent screens were evaluated as well. When toluene was employed as solvent, only trace amount of the desired product was detected (entry 6). Methylation did not reach in the presence of CH_3CN, and perform a relative low yield of in DMSO (entries 7 and 8). The yield of **2a** was dropped significantly in higher temperature such as 110 °C (entry 11), which would be suggested the decomposition of **1a** will be occurred in this reaction. In addition, the ratio of CO_2/N_2 in 1/1 would not affect the reactivity, which showed a good tolerance in low concentration of CO_2 (entry 13).

Table 1 Optimization of reaction conditions [a]

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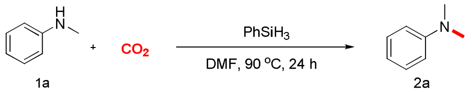
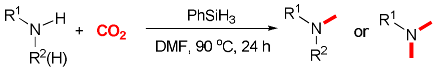


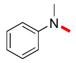
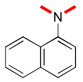
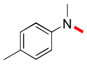
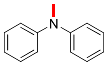
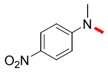
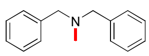
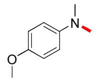
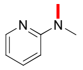
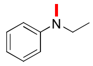
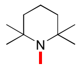
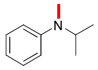
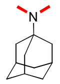
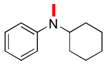
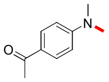
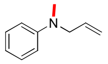
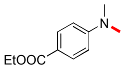
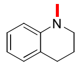
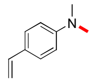
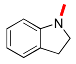
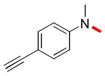
Entry	Variation from "standard conditions"	Yield%[a]
1	Ph_2SiH_2 instead of $PhSiH_3$	54
2	-	81(80)[c]
3	1.0 equiv. $PhSiH_3$	41
4	No CO_2	0
5	No $PhSiH_3$	0
6	Toluene instead of DMF	trace
7	CH_3CN instead of DMF	0
8	DMSO instead of DMF	45
9	DEF instead of DMF	61
10	60 °C instead of 90 °C	77
11	110 °C instead of 90 °C	26
12	$CO_2/N_2 = 1/7$	32
13	$CO_2/N_2 = 1/1$	81

[a] Sandard reaction conditions: **1a** (0.5 mmol), phenylsilane (1.0 mmol), DMF (3.0 mL), CO_2 (1 atm), 90 °C, 24 h. [b] Yield determined by by GC-MS using biphenyl as an internal standard. [c] The isolated yield is given in parentheses.

With the optimized conditions in hand, we further considered the scope of this methylation with various amines (Table 2). We firstly investigated the para-methyl substituent on the benzene moiety, showed no obvious influence on the reaction outcome (**2b**). Additionally, both electro-donating and -withdrawing groups were tolerated affording the expected products in moderate yields (**2c** and **2d**). When secondary amines substituted with alkyl groups, such as isopropyl, cycloalkyl, and cyclic amines were used as substrates, the desired products were obtained in 73-95% yield (**2e-j**). Moreover, primary amine was compatible with the reaction conditions as well, albeit dimethylated product was obtained in 47% yield (**2k**). Furthermore, diphenylamine could undergo this methylation, 34% yield of the desired **2l** can be gained. A heterocyclic compound, 2-methylaminopyridine was also amenable to this protocol (**2n**). Encouraged by the above results, we then explored the aliphatic amines. To our delight, the expected reactions occurred smoothly with satisfying yields (**2o** and **2p**). Moreover, this methylation reaction can tolerant the oxidizing groups (**2q-t**) as well.

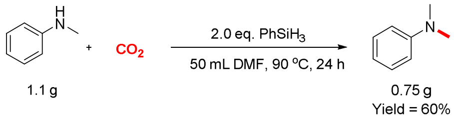
Table 2 Methylation of amines with CO_2 and phenylsilane [a]



2	Product	Yield (%) [b]	2	Product	Yield (%) [b]
2a		80%	2k		47%
2b		70%	2l		34%
2c		49%	2m		59%
2d		45%	2n		34%
2e		80%	2o		95% [c]
2f		95%	2p		70% [c]
2g		88%	2q		60%
2h		87%	2r		69%
2i		77%	2s		38%
2j		73%	2t		58%

[a] **1** (0.5 mmol), phenylsilane (2 eq. to amine moiety), DMF (3.0 mL), CO_2 (1 atm), 90 °C, 24 h. [b] Yield of isolated product. [c] Yield determined by ^{1}H-NMR using dibromomethane as an internal standard.

As a proof of the versatility and applicability of the presented methodology, this reaction could be run on gram scale (Scheme 2). The desired product **2a** was obtained in 60% yield (0.75 g) by using 2 eq. $PhSiH_3$ in 50 mL DMF (See in the Supporting Information).



Scheme 2 Gram scale reaction

To gain some preliminary insight into the reaction mechanism, several control experiments were carried out under the standard conditions (Scheme 3). Some previous works suggested[13,16] that the formation of formamide could be the main intermediates in both metal catalyst and organocatalyst introduced methylation reaction system. Yet, in our catalyst-free case, we only got the starting reactant quantitatively when *N*-methyl-*N*-phenylformamide (**3a**) was used as the substrate in CO_2 or N_2 atmosphere, indicating that the reaction was not through formamide as the intermediate in our case.

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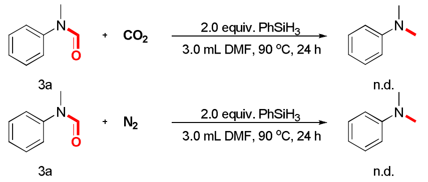
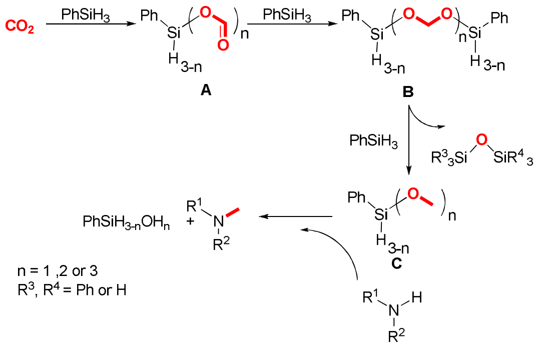


Scheme 3 Preliminary mechanistic studies

A possible reaction pathway was proposed in Scheme 4. Firstly, phenylsilane was converted into formoxysilane **A** in CO_2 atmosphere. Then with the additional $PhSiH_3$ was introduced, **A** tended to form the bis(silyl)acetal intermediate. Subsequently, intermediate **B** went through a deoxygenative reduction coupling in the presence of $PhSiH_3$ to afford the silyl methoxide intermediate **C** accompany with the silyl ether was released. Thus, the reduction of CO_2 to a silyl methoxide intermediate proceeded in a three-step process which was also suggested by Zhang et al. and Wang et al.[17,18] Moreover, when a highly polar aprotic solvent, such as DMF, was used, the activity of Si-H bond and the solubility of CO_2 could be promoted through solvation and polarization.[19] Finally, the resulting methyl group on the silyl methoxide was attacked nucleophilically by amine (**1a**) to furnish the desired methylamine.



Scheme 4 Proposed mechanism

Thus, in order to prove the intervening route of this reaction, ^{13}C-NMR spectra were exploited (See the Supporting Information). Interestingly, as $PhSiH_3$ was dissolved in d^6-DMSO under an atmosphere of CO_2 after 1 h, an 163 ppm peak was found, which could be indicated that formoxysilane intermediates, $(OCHO\text{-})_nSiH_{3\text{-}n}Ph$(**A**)[13,20] was formed in this reaction. Additionally, a peak at 55 ppm of $(CH3O\text{-})_nSiH_{3\text{-}n}Ph$ (**B**) was observed, with this result, we could suggest the reaction would be through the conversion of CO_2 to $(CH3O\text{-})_nSiH_{3\text{-}n}Ph$ (Fig. 1).[17] And when we used $PhSi(OMe)_3$ instead of $PhSiH_3$ and CO_2, the methylated product was also detected.

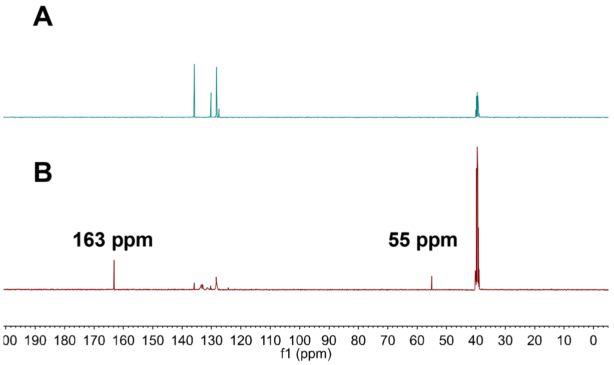
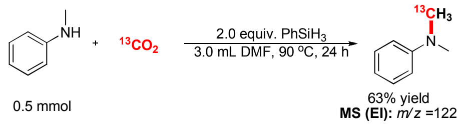


Figure. 1 ^{13}C-NMR spectrum of a) $PhSiH_3$ in d^6-DMSO, b) the reaction of CO_2 with $PhSiH_3$ in d^6-DMSO

Meanwhile, $^{13}CO_2$-labelled experiment has been conducted with *N*-methylaniline (Scheme 5). The corresponding ^{13}C-labelled methylation product was characterized by EI-MS and isolated in 63% yield. With this evidence, we can directly demonstrate the carbon source was provided from CO_2. (See in the Supporting Information).



Scheme 5 Labelling experiment

Conclusions

In conclusion, we have developed a catalyst-free protocol for the methylation of N-H bond by using CO_2 as a C1 building block under mild conditions. In this simple system, a variety of aromatic and aliphatic, secondary and primary amines could be directly converted into desired methylated products in moderate to good yields. Further studies will be focused on the mechanistic investigation. The exploration on the applications of this system is currently in progress and will be reported in due course.

Acknowledgement

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