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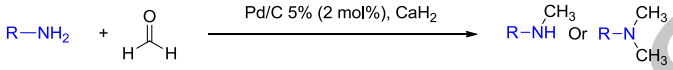

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Reductive *N*-methylation of amines with calcium hydride and Pd/C catalyst

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ABSTRACT

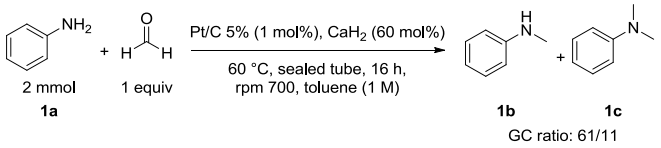
The methylation of amines by paraformaldehyde in the presence of calcium hydride as source of hydrogen and palladium on charcoal as catalyst was studied. Depending on the quantity of paraformaldehyde, monomethylated and dimethylated amines were selectively and efficiently prepared in one pot with good yields.

Amines are ubiquitous in nature. Secondary amines are important as they are used in pharmaceutical as well as agrochemical domains.[1] Specifically, secondary monomethylated amine moiety can be found in a number of natural products and drugs[2] such as ephedrine and methamphetamine for the most known or duloxetine and atomoxetine. Different methods are available to synthesise secondary monomethylated amines. The alkylation of primary amines using electrophile alkylating agents would be a straight forward method.[3] However, it generally does not stop at the monoalkylation and provides a mixture of secondary, tertiary amines and quaternary ammonium. Other drawbacks of such strategy concern the production of wastes and the use of toxic halides. Selectivity for the monoalkylation of primary amine was reported under specific conditions such as special electrophile alkylating agents,[4] special solvent[5] or use of cavitands.[6] A very selective route although time consuming is the use of protection / methylation / deprotection strategy using for example a benzyl,[7] an acetamide[8] or a nosyl[9] protecting group or an intermediate benzothiazol-2(3*H*)-imines.[10]

Another class of reaction to reach monomethylation of primary amine is based on reduction. Formylation or acylation of amine followed by its reduction using hydrides led to the corresponding monomethylated amines in good yields and selectivities.[11] The increase interest to develop environmentally friendly solutions, led to the use of other source of C1 such as CO_2 and methanol. Although promising results have been reported, the scope and / or selectivity for the *N*-methylation of primary amine are still limited. Hydrogen borrowing system has received a lot of interest. The monomethylation of alkylamine with methanol was described by Grigg in 1981 in the presence of a rhodium catalyst.[12] Later, Kagiya reported the dehydrogenation-reduction reaction with a Pt/TiO_2 heterogeneous catalyst at room temperature. In this report, the selectivity in favour of the monomethylated amine is lower than the Grigg's results.[13] The monomethylation of aniline with iridium[14] and ruthenium[15] catalyst in basic media was efficiently performed. Supercritical MeOH was also employed as methylating agent and a condensed carrier medium to selectively *N*-methylate in the presence of mixed oxide.[16] The increase interest in the valorisation of CO_2 is probably responsible for its use as methylating agent of amine in the presence of hydrogen and a ruthenium, palladium or copper catalyst.[17]

The most widespread methodology to prepare methylated amines is the reductive amination probably inspired by the pioneer work of Leuckart and Eschweiler-Clarke.[18] The selective monomethylation with formaldehyde and formic acid is difficult and only moderate selectivity is obtained with specific substrate.[19] Ammonium formate was also associated to palladium on charcoal to methylate aniline with a moderate yield.[20] Different reduction systems were explored in the reductive amination pathway: metals,[21] boron hydrides[22] and hydrogen.[23] From literature data, among the boron hydrides the reagent of choice is sodium triacetoxyborohydride notably for its lower toxicity compare to others.[24] Nevertheless, if the substrate is soluble in water or in alcoholic solvents sodium cyanoborohydride[25] or sodium borohydride will be used. In the latter case, the preformation of the imine is necessary in reason of the reactivity of this hydride with ketone.[26] Another reagent, the triphenylphosphonium tetraborate, prepared from sodium borohydride was also employed to carry out monomethylation in good yield.[27] We previously noticed that calcium hydride was scarcely studied as reducing agent for the reduction of organic functional groups. Nevertheless, we demonstrated the interest of such reagent to perform reductive alkylation[28] and amination.[29]

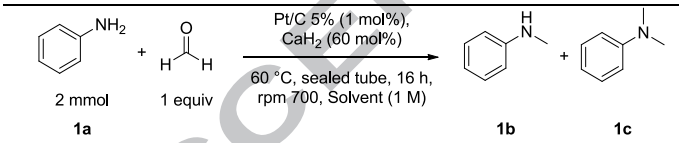
Amongst these transformations, the selective monomethylation of primary amine is one of the most challenging, although numerous methods have been reported as mentioned in the introduction part. In addition, the development of environmentally friendly conditions is an important issue. Calcium derivatives are not considered to be toxic and this element is the 5th most abundant element in the earth's crust. Consequently, we have been interested in studying the monomethylation of primary amines under the conditions we developed previously for the reductive amination, as a starting point. More precisely, paraformaldehyde was mixed with a stoichiometric quantity of aniline in the presence of 1 mol% of Pt/C 5% and calcium hydride (60 mol%) at 60 °C in toluene in a sealed tube (Scheme 1). The aniline was used as starting material for the optimization part.



Scheme 1. Methylation of aniline

Under these conditions the major product of the reaction was *N*-methylaniline **1b** (61% by GC) and aniline was not completely converted (24% remaining by GC). In order to increase both conversion and selectivity, first, the influence of the solvent was studied. Toluene was substituted by 2-MeTHF, methylcyclohexane and *tert*-butanol (Table 1). The ratio between *N*-methylaniline **1b** and *N*,*N*-dimethylaniline **1c** varied from 82:18 to 85:15 showing the weak influence of the nature of the solvent on the reaction selectivity. The conversion was more sensitive and decreased with 2-MeTHF and *tert*-butanol from 76% to 67% and 56% respectively (Table 1, entries 2 and 4). Toluene was chosen as solvent for the rest of the study. Methylcyclohexane was considered too nonpolar which may have caused solubility issue for the study of the scope.

Table 1. Influence of the solvent

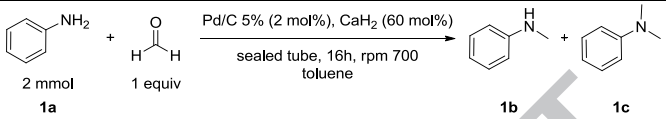


Entry	Solvent	Conversion[a] (%)	Ratio Mono **1b**:Di **1c**[a]
1	toluene	76	85:15
2	2-MeTHF	67	82:18
3	Mecyclohexane	77	83:17
4	*tert*-butanol	56	85:15

[a]The conversions and the ratios between *N*-methylaniline **1b** and *N*,*N*-dimethylaniline **1c** (Ratios Mono **1b**:Di **1c)** were determined by GC with dodecane as internal standard.

As we previously observed reductive amination with palladium on charcoal, this catalyst was introduced instead of platinum. A better result was obtained at this concentration as the conversion reached 80%. Moreover to improve the selectivity for the *N*-methylaniline **1b** over the *N*,*N*-dimethylaniline **1c,** the concentration of the substrate was decreased from 1 M to 0.5 M. However, only a slight decrease of the selectivity was observed which could be attributed to a decrease of the reaction rate. At this concentration (0.5 M) with 2 mol% of palladium of charcoal 84% conversion was observed with a ratio mono/di of 85:15 (Table 2, entry 1). The modification of the quantity of aniline compared to formaldehyde was deleterious for the conversion and the selectivity. The optimization was pursued with Pd/C 5% (2 mol%) as catalyst and a concentration of substrate of 0.5 M (Table 2).

Table 2. Optimization

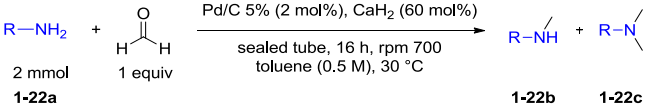


Entry	Modification	Conversion[a] (%)	Ratio Mono **1b**:Di **1c**[a]
1	Reaction at 60 °C	84	85:15
2	Preformation of the imine	80	75:25
3	Addition at 0 °C then 60 °C	84	86:14
4	Reaction at 80 °C	80	59:41
5	Reaction at 30 °C	95	89:11

[a]The conversions and the ratios between *N*-methylaniline **1b** and *N*,*N*-dimethylaniline **1c** (Ratios Mono **1b**:Di **1c)** were determined by GC with dodecane as internal standard.

Then, a sequential addition of the reagents was envisaged (Table 2, entry 2). More precisely, the amine was stirred with paraformaldehyde in toluene in the presence of 30 mol% of calcium hydride for 2 hours then, 30 mol% of calcium hydride and Pd/C were added. The preformation of the imine did not allow an increase of neither the conversion nor the selectivity. As the reaction was exothermic when the calcium hydride was introduced, the addition was performed at 0 °C then the reaction mixture was heated at 60 °C (Table 2, entry 3). In this case the conversion and the selectivity were unchanged compared to those performed at 60 °C (Table 2, entries 1 and 3). After the addition temperature, the influence of the reaction temperature was investigated. Increasing the reaction temperature from 60 °C to 80 °C increased the formation of the dimethylated product from 15% to 41% (Table 2, entries 1 and 4). Finally, decreasing the temperature from 60 °C to 30 °C gave the best results with a conversion increasing from 84% to 95% and a ratio monomethylated product **1b**:dimethylated product **1c** increasing from 85:15 to 89:11 (Table 2, entries 1 and 5).

The following conditions were selected to perform the monomethylation: to one equivalent of an amine with one equivalent of paraformaldehyde in toluene (0.5 M) was added calcium hydride (60 mol%) followed by palladium on carbon 5% (2 mol%) and the reaction was stirred at 30 °C for 16 hours (Scheme 2).



Scheme 2. Methylation of amines

Different amines were tested under these conditions to explore the scope and limitations of the method (Table 3). To collect a maximum of data for each reaction, the crude was analyzed by GC and NMR as follows: 1) the crude was suspended in ethyl acetate, 2) filtered through a pad of celite, 3) volume of the filtrate was completed to 250 mL with ethylacetate, 4) analyzed by GC. 5) After concentration the chlorohydrate salt were prepared, 6) and NMR yields were calculated by the addition of 3-bromotoluene as internal standard. Aniline **1a** was converted at 92% according to GC. NMR analysis showed a NMR yield of *N*-methylaniline **1b** of 63% and selectivity for **1b** of 90% (Table 3, entry 1). Important electronic effects were observed according to the nature of the substituents on the anilines (Table 3, entries 1-10). Electrondonating groups on aniline led to a decrease of the selectivity in *N*-monomethylated anilines **b** (Table 3, entries 1-4). For example, a methyl in para position led to a decrease of 10%

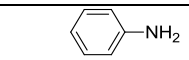
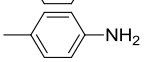
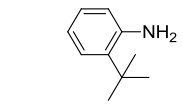
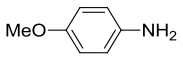
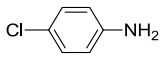
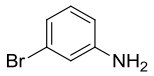
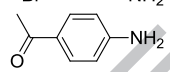
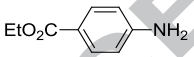
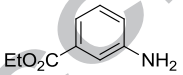
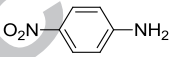
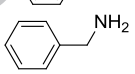
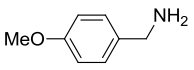
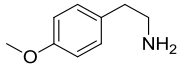
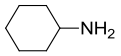
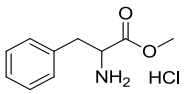
in *N*-monomethylation selectivity (Table 3, entries 1 and 2). Hindrance at the 2 position of the aniline, as for example 2-*tert*-butylaniline **3a**, did not impair the reactivity since 91% conversion was obtained as with 4-methylaniline **2a** (Table 3, entries 2 and 3). The selectivity for the monomethylated product was improved from 79% to 100% respectively for the 4-methylaniline **2a** and 2-*tert*butylaniline **3a**. In the case of the 4-methoxyaniline, a decrease of 20% selectivity for the monomethylation was observed (Table 3, entries 1 and 4).

Anilines bearing electron withdrawing groups, esters in this case, led to good 83% and 87% conversions and selectivity of 92% for the monomethylated products and this indifferently of their position around the aromatic core (Table 3, entries 8 and 9).

Considering the functionality tolerance, ester and ether remained unreacted while halides and ketone were partially reduced (Table 3, entries 4-9). Partial dehalogenation was observed as side reaction when anilines bearing halides were used: aniline **1a** and *N*-methylaniline **1b** were formed (Table 3, entries 5 and 6). *N*-Methylaniline **1b** was formed in 4% and 10% NMR yields in the reaction of 4-chloroaniline **5a** and 3-bromoaniline **6a** respectively. Low conversions were observed in GC of 37% and 26% respectively. This inhibition could be attributed to the halide salts generated which are known to reduce Pd/C reactivity.[30] In the case of the *p*-aminoacetophenone **7a**, the reduction of the ketone functionality to the corresponding ethyl group was an important side reaction, 29% by GC area (Table 3, entry 7). The main product of deoxygenation was *N*,*N*-dimethyl-4-ethylaniline estimated at 26% by GC area. This reduction has been already observed by our group in the presence of palladium on carbon. It is specially favored in the presence of electron donating group which is explaining why the main side product is the *N*,*N*-dimethyl-4-ethylaniline.[31] The reaction of 4-nitroaniline **10a** led to a low conversion of 22% determined by GC area in unidentified products of reduction. No products of reductive alkylation were detected (Table 3, entry 10).

Benzylamines gave lower selectivities for the monomethylated products from 46 to 66% (Table 3, entries 11 and 12). Alkylamines led to selectivities from 49 to 69% (Table 3, entries 13 and 14). Finally, amino acids were investigated. Reaction with phenylalanine methyl ester hydrochloride **15a** in the presence of 120 mol% of calcium hydride instead of 60 mol%, due to the use of the hydrochloride salt, gave a good selectivity in the monomethylated product **15b** of 79% (Table 3, entry 15).

Table 3. Scope of the reaction under the selected conditions[a]

Entry	Amine (**1-22a**)		Conversion (%)[b]	NMR yield Mono **b** (%)[b] (Isolated yield in **b**)[c]	Ratio Mono **b**:Di **c**[b]
1		**1a**	92[d]	63	90:10
2		**2a**	91[d]	64	79:21
3		**3a**	91[d]	91 (63%)	100:0
4		**4a**	75	50	70:30
5		**5a**	37[d]	12	100:0
6		**6a**	26[d]	11	ND[e,f]
7		**7a**	72[d]	38[d]	91:9[d]
8[g]		**8a**	74	75 (44%)	92:8
9		**9a**	87	80 (80%)	92:8
10		**10a**	22[d]	0	ND[e]
11		**11a**	78	22	46:54
12		**12a**	77	44	66:34
13		**13a**	87	38	49:51
14		**14a**	75	44	69:31
15[h]		**15a**	77	53	79:21

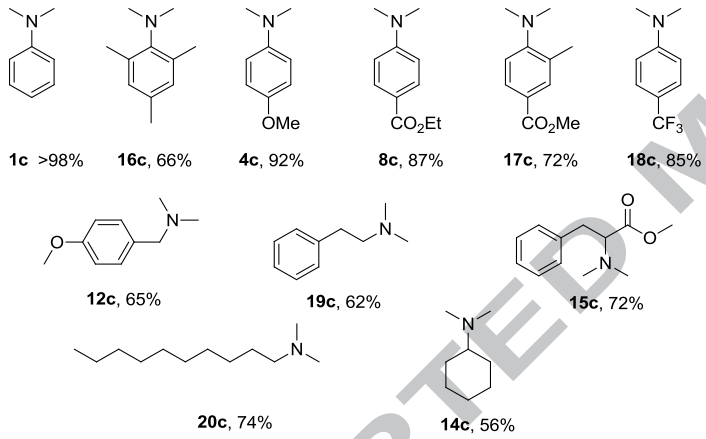
[a]In a sealed tube was introduced an amine (1 equiv), paraformaldehyde (1 equiv) in toluene (0.5 M) followed by the addition at room temperature under of argon of palladium on carbon 5% (2 mol%) and then calcium hydride (60 mol%). The pressure tube was closed and introduced in a preheated oil bath at 30 °C where it was stirred for 16 hours at 700 rpm; [b]Unless otherwise stated the conversions, yields in *N*-monomethylated amine and the ratio Mono **b**:Di **c** were determined by ^{1}H NMR analysis using 3-bromotoluene as internal standard; [c]Isolated yields refer to the yield of the *N*-monomethylated product after column chromatography; [d]Estimated by GC (percentage of GC area); [e]ND = not determined; [f]10% *N*-methylaniline was also detected in NMR analysis; [g]1.1 equiv of methyl 4-aminobenzoate was used instead of 1 equiv. [h]1.3 equiv of calcium hydride was used instead of 0.6.

With these tools in hands, we explored the access to the *N*,*N*-dimethylamines. The reaction conditions developed for the monomethylation were used with slight modifications; the quantities of paraformaldehyde and calcium hydride were respectively increased to 2.5 and 2 equivalents with respect to the starting amine. Change of the reaction temperature from 30 °C to

80 °C and solvent from toluene to CPME (cyclopentylmethyl ether) improved the yield up to 98%.

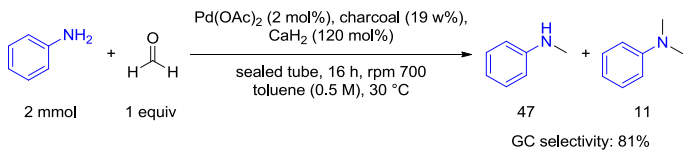
In most cases, when the amines were isolated as chlorohydrate salts, poor yields were observed. However, the corresponding oxalic acid salts were isolated in good to excellent yields (56-98%, Scheme 3). The crude reaction mixture was diluted in diethyl ether and filtered through a pad of celite. To this solution an ethanolic solution of oxalic acid was added, allowing the precipitation of the corresponding *N*,*N*-dimethylammonium oxalate salts. For example, *N*,*N*-dimethylanilinium oxalate **1c** was isolated in high yields (>98%) both from the reaction of aniline **1a** and *N*-methylaniline **1b**. Anilines were converted to the corresponding *N*,*N*-dimethylammonium salts **16c**, **4c**, **8c**, **17c** and **18c** in good to excellent yields (from 66% to 92%). Although, quick look at the results may not show strong electronic effects, it seems that anilines bearing electrondonating group lead to higher yields than the ones bearing electronwidrawing group (for example **4c**, 92% *versus* **18c**, 85%). In contrast, steric hindrance may play a bigger effect; the anilines bearing *ortho* substituents lead to ammonium salts in moderate yields (**16c** in 66% and **17c** in 72%).

The same reaction conditions can be applied to the primary alkylamines, albeit in lower yields than anilines (**12c**, **19c**, **15c**, **20c**, **14c** in 56-74%).



Scheme 3. Dimethylation of amines

Quality of palladium on carbon differs often from suppliers and batches creating reproducibility issues and use of a higher loading of catalyst than necessary (>5 mol%). Hence, we investigated the *in situ* generation of palladium (0) on charcoal from $Pd(OAc)_2$ and charcoal inspired by the work of Felpin and Fouquet.[32] We carried out the reaction of aniline with paraformaldehyde under the optimized conditions of monomethylation using $Pd(OAc)_2$ (2 mol%) and the quantity of calcium hydride was raised to 120 mol% in order to have enough reductant for the *in situ* reduction of $Pd(OAc)_2$ (Scheme 4). The conversion and selectivity for *N*-methylaniline were lower than with commercially available Pd/C. A conversion of aniline **1a** of 58% was observed and a selectivity for the *N*-methylaniline **1b** of 81% *versus* 92% conversion and 90% selectivity with commercial Pd/C.



Scheme 4. Methylation of amine with Pd(0) generated *in situ*

In conclusion, the monomethylation of amines with paraformaldehyde in proportions close to the stoichiometry in the presence of CaH_2 as source of hydrogen and palladium on carbon as catalyst has been studied. Selectivity in monomethylated products from 46 to 100% has been observed on different amines (anilines, benzylamines, alkylamines and amino acids) over 15 examples. With an increase of the quantity of paraformaldehyde and calcium hydride, dimethylated amines were also synthesized in good isolated yields.

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References and notes

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Highlights

- The methylation of amines is performed with paraformaldehyde, CaH_2 and Pd/C
- An easy-to-handle procedure applied to aniline and primary alkylamines
- In situ hydrogen production from calcium hydride and water