Additive-free Pd/In_2O_3 Catalyzed *N*-methylation of Primary Amides using Formic Acid

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Abstract: Here we report on the use of formic acid as a green and safe reagent for the N-methylation of primary amides in the presence of a Pd/In_2O_3 solid catalyst. No additive is needed and primary amides are selectively N-methylated in good to excellent yields. The reaction operates through a formylation/reduction pathway, leaving the amide carbonyl untouched.

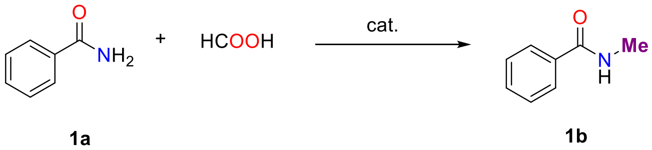
Introduction

N-methylated amides are present in numerous natural products and in a large variety of pharmaceuticals[1] including valuable peptides[2]. Methylation of an amide in a drug molecule can have a strong effect on its lipophilicity and potency.[3] In this context, the development of efficient and reliable methodologies for the methylation of amides is of particular interest. Amides have poor nucleophilicity, thus poor reactivity towards N-methylation, and only few methods have been reported. Traditional methods involve stoichiometric quantities of highly toxic reagents such as iodomethane[4], dimethylsulfate[5] or chloromethyldimethylsilyl chloride.[6] In the last decade, strategies involving peroxides and Cu[7], or Pd/Ni[8] molecular catalysts were described. Methods utilizing stoichiometric quantities of mild reagents with lower toxicity were also introduced in the last few years.[9] Methyl trifluoroacetate combined with a base was used for the chemoselective N-methylation of bifunctional secondary amides[10], and trialkyl phosphates with NaOH or BuLi were used for the non-catalytic monoalkylation of primary amides.[11] More recently, quaternary ammonium salts were reported to allow methylation of a variety of molecules, among them amides, with Cs_2CO_3 as a base.[3, 12] In the quest for more sustainable reactions, catalytic strategies involving alcohols for the alkylation of amides were developed.[13] The use of methanol, however, remains less explored. Kundu and co-workers recently reported the use of molecular catalysts of ruthenium[14] or cobalt[15] with a base for methylation of aromatic and aliphatic primary amides with methanol. They also achieved the synthesis of N-methylated amides from methanol and aldoximes[16] or nitriles[17] with ruthenium complexes. Last year, Tindari, Mandal *et al*. reported a method for the N-methylation of primary amides with CO_2, with a bicyclic (alkyl)(amino)carbine (BICAAC) as an organic catalyst and pinacolborane (HBPin) as a sacrificial reducing agent.[18] In this paper, we introduce a methodology for the catalytic additive-free N-methylation of primary amides with formic acid (FA), another C_1 reagent that can act as both a carbon source and a hydrogen source. A now mature technology has been developed to promote its synthesis from the 2-electron reduction of CO_2 in an electrochemical cell over electro-catalysts, making formic acid a renewable reagent.[19]

In a previous paper, we reported on the additive-free, one-pot methylation of secondary amines with formic acid as the sole carbon and hydrogen source and a Pd/In_2O_3 catalyst.[20] In an attempt to expand the use of formic acid as a renewable methylation reagent, it was important to test whether our catalytic system could promote methylation of more challenging substrates, like primary amides, which are less nucleophilic than amines. An additional difficulty in using formic acid for the methylation of amides is to prevent the reduction of the amide function under reducing conditions. To our delight, we observed were able to overcome these challenges and achieve the additive-free methylation of primary amides in moderate to excellent yields with a Pd/In_2O_3 solid catalyst.

Results and Discussion

Since Pd/In_2O_3 showed activity for the methylation of amines with FA, we decided to explore the reactivity of oxide-based catalysts doped with metals known for their catalytic reduction properties on the N-methylation of primary amides. In a first attempt, we tested our strategy with benzamide as a substrate, in DME and a catalyst loading of 5 wt.% of the doping metal. (Scheme 1) The catalytic reaction was conducted in a sealed autoclave under atmospheric argon pressure. The results obtained with various catalysts are listed in Table 1. The oxide-supported catalysts were synthesized by a wet impregnation method, followed by calcination of the powders at 400°C for 3h under air. Their performance was not improved by pre-reduction under H_2 (20 bar, 200°C, 1h), they were thus used as prepared. GC analysis of the atmosphere in the autoclave after 18h of reaction showed a significant presence of H_2 and CO_2, indicative of FA decomposition during the reaction, as well as traces of CO. (Fig. S1).



1a **1b**

Scheme 1. *N*-methylation of benzamide (**1a**) with formic acid.

In_2O_3 displayed limited activity and weak selectivity towards the desired product (Table1, entry 2). In_2O_3 doped with various metals (Pd, Pt, Ru, Fe, Mn, entries 3-7), displayed moderate to good activity and selectivity. Alumina doped with the same metals showed moderate activity, however benzoic acid was the main product (entries 8-12). No activity was recorded with Pd or Pt supported on carbon.

Table 1. Methylation of benzamide with FA over various catalysts[a]

Entry[b]	Cat.	Conv. (%)	Yield **1b** (%)[d]
1	None	30	<1
2	In_2O_3	54	8
3	Pd/In_2O_3	84	75
4	Pt/In_2O_3	54	49
5	Ru/In_2O_3	39	10
6	Fe/In_2O_3	48	9
7	Mn/In_2O_3	52	2
8	Pd/Al_2O_3	11	0
9	Pt/Al_2O_3	<1	<1
10	Ru/Al_2O_3	0	0
11	Fe/Al_2O_3	50	<1
12	Mn/Al_2O_3	45	<1
13	Pd/C	0	0
14	Pt/C	0	0

[a] Reaction conditions: **1a** (1 mmol), catalyst 5 wt% [active metal], FA (12 mmol), DME (10 mL), 200°C, 18 h. Yields determined by GC-MS using isooctane as an internal standard, after calibration.

The best results were obtained with Pd/In_2O_3 as a catalyst (entry 3). The reaction conditions for the methylation of various amides were therefore optimized with this catalyst (see Table S1). A screening of different solvents showed that dioxane is the best suited for the reaction (Table S1, entry 7). The benchmark reaction was conducted at 100, 150 and 200°C (Table S1, entries 1-3). We observed that there was no catalytic activity below 200°C. A reaction time of 18 h was retained. A longer reaction time (entries 9) did not provide a significant yield improvement.

Several methylation agents were tested (see Table S2). Formaldehyde yielded slightly better results than FA with the benchmark reaction in DME (entries 1 and 2). However, formaldehyde is toxic and difficult to handle, and the slightly better yield does not justify using it as a methylation agent with this method. Methyl formate and methanol yielded only 1% and 11% of the desired product respectively (entries 3 and 4).

The Pd/In_2O_3 catalyst we used for the N-methylation of primary amides is a dark brown powder. It turns to dark gray/black after being used in a reaction and keeps this color after it is annealed again under air, in a typical recycling experiment. XPS spectra were recorded for samples of the fresh, reacted, and recycled catalyst, and confirmed the presence of In, Pd and O in all three samples. (Fig. S2 and S3) In the as-synthesized catalyst, the Pd $3d_{5/2}$ peak was observed at 337.1 eV and was assigned to PdO.[21] The In $3d_{5/2}$ peak was observed at 444.7 eV characteristic of In_2O_3.[21] In the reacted catalyst, the Pd $3d_{5/2}$ signal was shifted to a lower value of 334.9 eV, which was attributed to elemental Pd. The In $3d_{5/2}$ was recorded at 444.4 eV. Indium was thus not significantly reduced during the reaction, however a broadening of the peaks was observed. This could indicate the presence of another chemical environment for In(III), possibly $In(OH)_3$. In the recycled catalyst, the Pd $3d_{5/2}$ peak was shifted back to 336.7 eV, indicative of an oxidation to PdO. The In $3d_{5/2}$ signal was observed at 444.5 eV, with narrowing of the peaks signaling a return to a single In_2O_3 phase. The atomic concentration of Pd of the near surfaced region evolved from 16.2% in the as-prepared catalyst, to 1.9% in the reacted catalyst and 2.2% in the recycled sample (Table S3).

The morphology of the fresh, used and recycled catalysts were investigated by transmission electron spectroscopy (TEM). The fresh Pd/In2O3 catalyst images show nanoparticles aggregates which size varies from 100 nm to 500 nm. The particles on the surface are smaller than the ones inside the aggregate, with an individual size of about 10 nm. (Fig.1, left). High-resolution TEM (HT-TEM) analyses indicate that particles aggregates present a crystalline structure (Fig. 1, right). Further analyses of the chemical composition were achieved by scanning-TEM (STEM) mode combined with energy dispersive X-ray (EDX) spectroscopy (Fig. S4). The results show that the aggregates of small particles on the peripheral zones have a higher concentration of Pd compared to In, while the particles aggregates in the center of the objects show reverse metal proportions. We can therefore hypothesize that the fresh Pd/In2O3 catalyst is composed of palladium oxide deposited on indium oxide, which is in accordance with the wet impregnation method used for synthesis. This is consistent, as well, with results we reported previously with other samples of the material.[20]

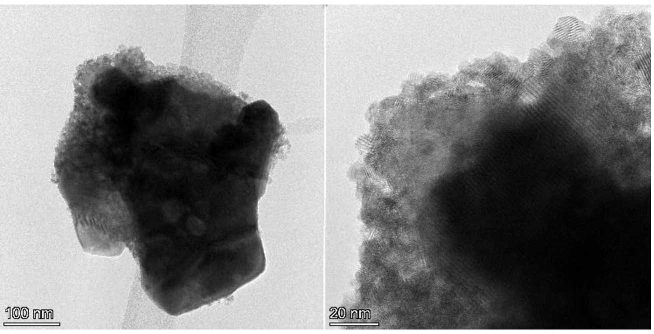


Figure 1. HR-TEM images of a particle of a fresh sample of Pd/In_2O_3 (left), and close-up (right) showing the crystallinity of the material.

Similar experiments were conducted on a sample of the reacted catalyst. (Fig. S5 and S6). The catalyst conserves similar morphology as the fresh sample, with small objects aggregated on seemingly bigger ones. HR-TEM confirms that the material is crystalline. EDX measurements showed an inhomogeneous density in Pd over of the catalyst. This is possibly due to initial chemical inhomogeneity of the fresh material. The high content of Pd detected on the surface of particles aggregates is not significantly homogenized with the indium-rich areas, unlike what was observed with amine methylation.[20] Analysis of a re-annealed sample of the catalyst confirmed that crystallinity is retained, and the content in palladium is not homogeneous over a catalyst particle (Fig. S7). Although some spots on the material display a high content in Pd, the XPS analyses show that the average Pd surface concentration on the surface of the material decreases over the reaction, and remains at about 2% after recycling. This could be explained by diffusion of Pd into the bulk of the material upon exposure of In_2O_3 to reductive conditions, as was reported by Neumann *et al*.[22]

From these observations we can propose that PdO in the catalyst is reduced during the reaction, either by FA or by H_2 produced upon FA decomposition. From these observations as well as from the testing of various catalysts, we can hypothesize that there is a synergy between the indium oxide support and the deposited palladium, and the catalyst is still active with low surface palladium concentrations.

Recycling experiments were carried out with benzamide as a substrate. After each run, the catalyst was recovered by centrifugation, thoroughly washed and annealed under air (400°C, 3h) before it was used again in a reaction under our preferred conditions. The activity and selectivity of the catalyst were retained upon 4 runs (Fig. 2)

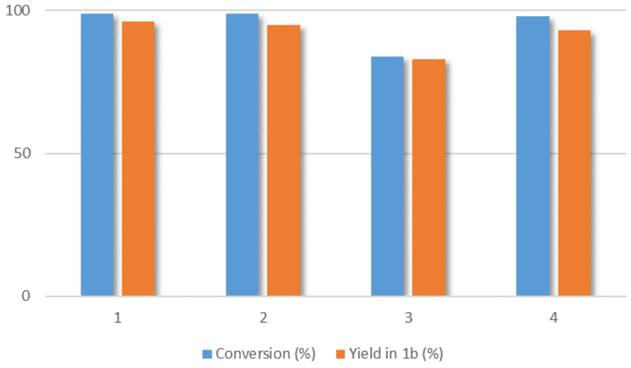
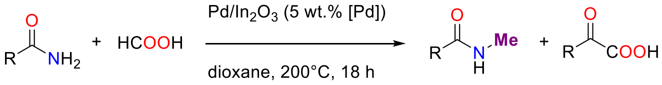


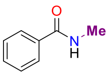
Figure 2. Conversion and yield in *N*-methylbenzamide (**1b**) after 1, 2, 3 and 4 runs.

The methylation of a variety of primary amides was carried out to explore the potential of this novel catalytic transformation. The results are gathered in Table 2. Using 12 equivalents of FA, methylation of aromatic primary amides (entries 1 to 10) was achieved in yields ranging from 30 to 96% (18h, 200°C, 5 wt.% [Pd]). The catalytic system tolerates a variety of substituents on the aromatic ring. For all substrates except **7a** and **9a**, the corresponding carboxylic acid was the only byproduct. With 4-bromobenzamide **7a** (entry 7), de-brominated side-products N-methylbenzamide and benzamide were observed as well, reducing the yield in the desired product. With **9a**, N,N-dimethyl(3-methoxy)benzamide was observed as a byproduct (15%). No reduction of the aromatic cycles was detected, as can be the case with Pd containing catalysts when aromatic amides are exposed to an hydrogen pressure.[23] Moreover, we did not observe the reduction of the amidic substrates to amines. Moderate catalytic activity was recorded with aliphatic substrates (entries11-12).

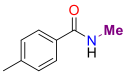
Table 2. *N*-methylation of primary amides with FA catalysed by Pd/In_2O_3.[a]



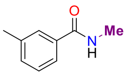
a **b** **c**



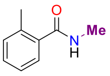
1b



2b



3b



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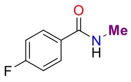

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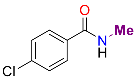

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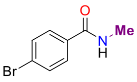
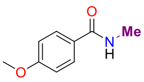
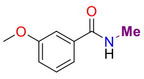


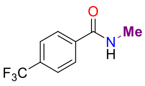
7b



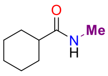
8b



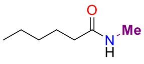
9b



10b



11b



12b

Entry	Substrate	Conv. (%)	Yield **b** (%)

1	**1a**	99	96 (92)
2	**2a**	96	84 (64)
3	**3a**	85	74 (64)
4	**4a**	99	91 (85)
5	**5a**	95	85 (77)
6	**6a**	92	80 (75)
7	**7a**	85	30
8	**8a**	91	84 (78)
9	**9a**	95	78 (74)
10	**10a**	92	85 (75)
11	**11a**	60	25
12	**12a**	65	5

[a] Conditions: substrate (1 mmol), FA (12 eq), Pd/In_2O_3 (5 wt.% [Pd]), dioxane, 200°C, 18 h. Yields determined by GC-MS Yields determined by GC-MS using isooctane as an internal standard, after calibration. Isolated yields in parentheses.

In light of these results we investigated possible reactions pathways and intermediates for the primary amides methylation reaction. As GC experiments showed, formic acid is partially decomposed to H_2 and CO_2 over Pd/In_2O_3 (Fig. S1). FA, H_2 and CO_2 are thus possible molecules taking part in the reaction. N-formylbenzamide was observed as an intermediate in our benchmark reaction by GC-MS and NMR. Traces of that molecule were observed under our preferred conditions in the absence of a catalyst as well. When benzamide was reacted with 50 bars of a H_2/CO_2 1:1 mix in the presence of Pd/In_2O_3 (200°C, 18h), no conversion of the substrate was observed. We can therefore hypothesize that formic acid is the vector of the formylation of benzamide. The direct reaction of N-formylbenzamide with H_2 (20 bar, 200°C, 18h) lead to complete conversion of the substrate to benzamide as the major product and N-methylbenzamide and benzoic acid as trace products. It seems therefore that the presence of formic acid in the reaction is necessary both for the formylation and the reduction steps. A highlight of this catalytic system is its ability to reduce the formyl group of the intermediate without reacting with the carbonyl group of the amide function.

Conclusion

In conclusion, we have developed a simple, additive-free method for the N-methylation of primary amides over a Pd/In_2O_3 solid catalyst. Aromatic primary amides are methylated in good to excellent yields, and the catalyst tolerates a variety of substituents. Formic acid, a renewable reagent, proves its usefulness as a methylation agent, allowing fruitful reaction with less reactive molecules and expanding the narrow scope of molecules capable of methylating amides.

Experimental Section

General considerations: commercially available products (Sigma-Aldrich or Acros Organics or Alfa Aesar or TCI Europe) were used without further purification. Dioxane was dried on Na/benzophenone.

Gas chromatography data were acquired with a Shimadzu GC2010 gas chromatograph; column: Carboxen 1010 PLOT fused silica capillary (30 m* 0.53 mm * 30 µm); injection temperature: 230°C; column temperature: 100°C; flow: 5mL/min; purge : 2mL/min; carrier gas: Ar; detector: TCD 203°C, 30 mA.

GC-MS data were collected on a Shimadzu GCMS-QP2010 Plus gas chromatograph equipped with a Supelco SLB^{TM}-ms fused silica capillary column (30 m*0.25 mm*0.25 µm) using He as a carrier gas.

NMR spectra were obtained on a Bruker Avance NEO 400 MHz spectrometer. Chemical shifts for the products were referenced to solvent impurities.

Catalysts preparation: In_2O_3 was obtained from Acros Organics and neutral Al_2O_3 from Thermo Fisher Scientific. M/In_2O_3 and M/Al_2O_3 (10 wt%. M, M = Pd, Pt, Ru) catalysts were prepared by an impregnation method using the nitrate salts. For the preparation of Pd/In2O3 as an example, 400mg $Pd(NO_3)_2.3H_2O$ were dissolved in 50 mL distilled water at room temperature. 1.4 g In_2O_3 were then added and the suspension was stirred for 3h. The suspension was then evaporated to dryness and the solid was let to dry overnight at 80°C. It was then annealed in air at 400°C for 3h.

Catalytic experiments: In a typical experiment, a 25 mL stainless steel autoclave equipped with a glass liner and a stirring bar was charged with 1 mmol of the substrate and the required quantity of catalyst to amount to 5wt.% [Pd] (or about 2.5 mol% [Pd]). The autoclave was then purged 4 times with Ar (5 bar). 10 mL dioxane and 450 µL FA (12 mmol) were then injected in the autoclave under inert conditions. The autoclave was heated for 18h at 200°C. It was then let to cool down to room temperature and depressurized, and the reaction medium was centrifuged. Conversions and yields were determined by GCMS with isooctane as an internal standard. The GCMS sensibility was calibrated using the commercial or the isolated products.

Purification of the methylated amides: To obtain the isolated products, the reaction mixture was cooled to room temperature and the catalyst was removed by centrifugation. The solvent was evaporated and the desired products were isolated by column chromatography over silica gel with dichloromethane/methanol.

Catalyst recycling experiments: After each run, the catalyst was separated by centrifugation, washed with 10 mL of acetone 3 times, dried in air and annealed at 400°C for 3 hours, then used directly for the next run.

Products identification: ^1H NMR and ^{13}C NMR spectra of the following isolated products were identical to reported data. **7b**, **11b**, **12b** were identified by GC/MS chromatography and by ^1H NMR and ^{13}C NMR from the crude mixture.

Acknowledgements

This work was supported by a grant from Fondation de la Maison de la Chimie (Paris, France). We acknowledge CEA, CNRS, and the European Research Council (ERC Consolidator Grant Agreement no.818260). The authors thank Dr Jocelyne Leroy (Université Paris-Saclay, CEA, CNRS, NIMBE – Gif-sur-Yvette, France) for the XPS measurements.

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