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N-Formylation of Amines Catalyzed by Nanogold under Aerobic Oxidation Conditions with MeOH or Formalin

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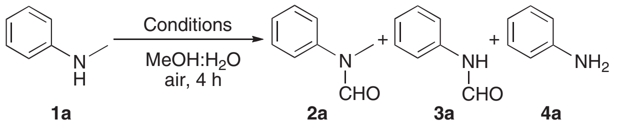
Gold nanoclusters stabilized by poly(*N*-vinyl-2-pyrrolidone) (**Au:PVP**) are active and selective catalysts for *N*-formylation of amines under aerobic oxidation using methanol or formalin as a formyl source.

Direct formation of amides from alcohols or aldehydes with amines has recently received attention from the viewpoint of the development of environmentally benign processes.[1] In particular, *N*-formylation of amines using MeOH or formaldehyde (especially formalin) is very important. The use of simple reactants makes it possible to understand the reaction mechanism. Furthermore, the starting materials are both economical and the formamide derivatives produced in the reaction are important intermediates in organic synthesis. Until now though, only a few examples of this transformation have been reported. Cu hydroxy salts have been used in the presence of hydrogen peroxide.[2] Aerobic oxidation has been achieved with nanosized-gold supported on metal oxide[3] with MeOH, and formylation of dimethylamine with formaldehyde has been carried out using metallic gold[4] or silver[5] surfaces as a catalyst. Practical procedures for *N*-formylation by aerobic oxidation that tolerate a wide scope of amines are still needed.

Nanosized-gold metal has recently attracted a great deal of interest because of its high activity[6] and potential application in the emerging area of green oxidation chemistry. We have recently demonstrated that gold nanoclusters stabilized by poly(*N*-vinyl-2-pyrrolidone) (**Au:PVP**) act as an excellent *quasi*-homogenous catalyst for the aerobic oxidation of benzylic alcohols,[7] generation of H_2O_2 in the presence of ammonium formate,[8] homocoupling reaction of arylboronic acids,[9] and other cyclization reactions.[10] Herein, we wish to report highly selective direct *N*-formylation using MeOH or formalin as a formyl source in the presence of **Au:PVP** under aerobic conditions.

Given our recent achievements in the aerobic oxidation of alcohol by **Au:PVP**,[7] we decided to conduct an *N*-formylation reaction similar to those used for methanol oxidation. *N*-Formylation of *N*-methylaniline was screened in MeOH/H_2O and the results are listed in Table 1.

Table 1. The reactions of **1a** under aerobic MeOH oxidation conditions



Entry	Conditions		Solvent ratio ($MeOH:H_2O$)	Temperature /°C	Yield[a]/%			
	Au:PVP /atom %	LiOH /mol %			**1a**	**2a**	**3a**	**4a**
1	10	—	1:2	reflux[c]	no reaction			
2	—	200	1:2	reflux[c]	no reaction			
3	10	200	1:2	reflux[c]	—	94	5	—
4	10	200	1:2	50	16	80	2	2
5	10	200	1:2	27	no reaction			
6	10	200	1:1	50	63	35	—	1
7	10	200	1:0	50	no reaction			
8	5	200	1:2	reflux[c]	9	81	6	4
9[b]	5	200	1:2	reflux[c]	2	89	8	2

[a]GC yields using hexadecane (C_{16}) as an internal standard. [b]Reaction time: 8 h. [c]Bath temperature: 80 °C.

The reaction did not proceed without either base (Entry 1) or **Au:PVP** (Entry 2). The basic conditions are important for oxidation of MeOH to generate the key intermediate for *N*-formylation. The best results were obtained when 200 mol % of LiOH was used and LiOH was included in all further reactions.[11] Reaction temperature was then evaluated. The reaction proceeded smoothly in the presence of 10 atom % of **Au:PVP** under reflux conditions (Entry 3),[12] giving *N*-formyl-*N*-methylaniline (**2a**) in 94% yield along with the formation of *N*-formylaniline (**3a**) in 5% yield, which is produced via oxidative demethylation followed by *N*-formylation. The reaction also proceeded at 50 °C and the yields of the products, **2a**, **3a**, and aniline (**4a**) after 4 h were 80%, 2%, and 2% yields, respectively with **1a** also recovered in 16% yield (Entry 4). No reaction was observed at 27 °C (Entry 5). The importance of water and the amount of catalyst were then investigated. It was found that the amount of H_2O is crucial in this reaction. When a 50/50 MeOH/H_2O mixture was used as the solvent at 50 °C for 4 h (Entry 6), the reaction rate drastically decreased and the yield of **2a** declined to 35%, while **1a** was recovered in 63% yield. In addition, no reaction occurred in 100% MeOH solution (Entry 7). When the amount of catalyst was reduced to 5 atom %, the conversion yields after 4 and 8 h were 91% and 98%, respectively, and the yields of by-products **3a** and **4a** slightly increased, as shown in Entries 8 and 9.

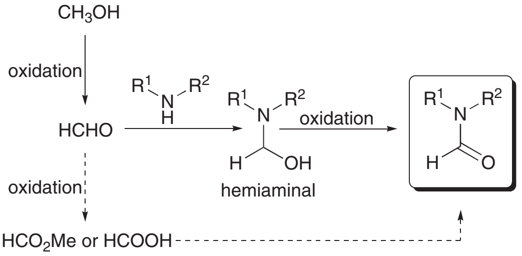
Aerobic oxidation of MeOH with Au catalysts[3] affords formaldehyde (HCHO), formic acid (HCOOH), methyl formate (HCOOMe), or carbon dioxide (CO_2). To clearify the possible intermediate in the formylation reaction, different formyl sources were substituted for MeOH. The results are represented in Table 2.

The reactions were carried out in EtOH:H_2O (1:2) under conditions analogous to those used with MeOH:H_2O (1:2) as the solvent, except that the temperature was lower (50 °C) to avoid

Table 2. Variation of formyl source

Entry	Conditions[a]		Temperature /°C	Yield/%[b]			
	Au:PVP /atom %	Formyl reagent /100 mol %		**1a**	**2a**	**3a**	**4a**
1	10	—	50	no reaction			
2	10	HCHO	50	21	81	—	1
3	10	HCOOMe	50	no reaction			
4	10	HCOOH	50	no reaction			
5[c]	1	HCHO	27	—	97	—	—

[a] Conditions: 0.05 mmol *N*-methylaniline, 200 mol % LiOH, EtOH:H_2O (1:2), under air, 1 h. [b] GC yields using hexadecane (C_{16}) as an internal standard. [c] Conditions: 150 mol % HCHO, 100 mol % NaOH, 9 h.



Scheme 1. Possible formyl source diagram for *N*-formylation of amine and methanol.

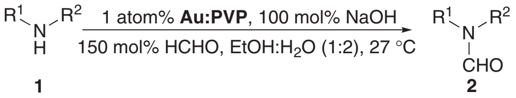
N-acetylation via oxidation of ethanol to acetaldehyde. No reactions took place in the absence of a formyl source (Entry 1). In all of the other reactions listed in Table 2 except Entry 5, 100 mol % of various kinds of formyl reagents were added. The *N*-formylation product **2a** was obtained in 81% yield in the presence of formalin (Entry 2). In contrast, no reaction occurred in the presence of HCOOMe or HCOOH (Entries 3 and 4). These results strongly suggest that a possible reaction pathway might involve the formation of a hemiaminal by the reaction of formaldehyde with amine, which is then further oxidized by **Au:PVP**, rather than proceeding via oxidation of MeOH to a formic acid equivalent followed by amidation (Scheme 1).

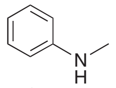
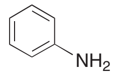
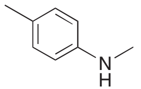
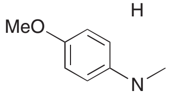
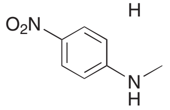
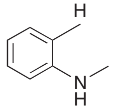
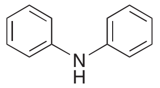
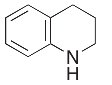
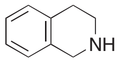
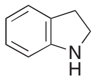
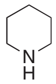
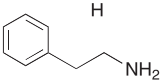
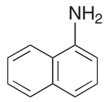
These results are not consistent with a report on the reaction on heterogeneous Au/NiO published by Ishida and Haruta.[3] They found that Au/NiO catalyzed the oxidation of MeOH to HCO_2Me under conditions (0.5 MPa O_2, 100 °C, 5 h) where it might react with benzylamine to give the *N*-formyl product. On the other hand, Friend et al. proposed the existence of a hemiaminal intermediate in the reaction of dimethylamine and formaldehyde on the surface of O/Au.[4] Also, a hemiaminal intermediate has been considered in a reaction on a Ag catalyst.[1e,5]

Since the rate determining step would be the aerobic oxidation of MeOH to formaldehyde, and the oxidation of the hemiaminal to amide would occur smoothly, the reaction conditions were expected to be much milder in the presence of formalin compared to MeOH. In fact, when 150 mol % HCHO was used, the *N*-formamide **2a** was obtained almost quantitatively (97% yield) at 27 °C for 9 h, even with only by 1 atom % of **Au:PVP** (Entry 5, Table 2).

The above result motivated us to develop a practical method for *N*-formylation of amines with formalin under aerobic conditions catalyzed by **Au:PVP**. Typical reaction conditions are as follows: 1 atom % of **Au:PVP**, 100 mol % of NaOH, 150 mol % of HCHO (added as a 37% formalin solution), EtOH:H_2O (1:2), 27 °C, 9 h.[12] The results of this reaction with various amines are summarized in Table 3.

Table 3. Scope and limitation of *N*-formylation catalyzed by **Au:PVP**



Entry	Amines		Isolated yield/%
1		**1a**	97
2		**1b (4a)**	53 (96[a])
3		**1c**	>99
4		**1d**	86
5		**1e**	no reaction
6		**1f**	no reaction
7		**1g**	2
8		**1h**	95
9		**1i**	81
10		**1j**	98[a]
11		**1k**	88 (>99[b])
12		**1l**	87
13		**1m**	78[a]

[a] 10 atom % **Au:PVP** was used. [b] 5 atom % **Au:PVP** was used.

Reaction of **1b** was slightly different from that seen with **1a** (Entry 1). Aggregation of the Au clusters was observed to occur gradually as the reaction proceeded, leading to only 53% yield in the presence of 1 atom % of **Au:PVP**. The yield was improved up to 96% when the amount of catalyst was increased to 10 atom % (Entry 2). A remarkable electronic effect was observed in the reaction with *para*-substituted *N*-methylaniline derivatives. Anilines with an electron-donating group (**1c** and

1d) afforded the *N*-formyl products **2c** and **2d** in excellent yields (>99% and 86% of **2c** and **2d**, respectively). On the other hand, no reaction was observed in the case of *para*-nitro derivative **1e** due to the strong electron-withdrawing effect. It was also found that the reaction is susceptible to steric effects, a characteristic that has often been observed in previous studies.[9] *N*-Formylation did not proceed for *N*-methyl-*ortho*-toluidine (**1f**) and only 2% of desired product **2g** was obtained from diphenylamine (**1g**) as shown in Entries 6 and 7.

Except for these cases, the formylation reaction conditions were applicable to many types of amines. Cyclic arylamines **1h**–**1j** in Entries 8–10 proceeded to give the desired products **2h**–**2j** in high yields (81–98%). In addition, piperidine (**1k**) also underwent *N*-formylation in excellent yield (88%, Entry 11) in the presence of 1 atom % of **Au:PVP** and quantitative yield when 5 atom % **Au:PVP** was used. As for primary amines, alkylamine **1l** in Entry 12 underwent *N*-formylation to furnish **2l** in 87% yield, and α-naphthylamine **1m** in Entry 13 also gave the product **2m** in 78% yield.

As described above, **Au:PVP** was found to be an excellent catalyst for the direct *N*-formylation of amine with MeOH or formalin as a formyl source. In particular, only 1 atom % of catalyst was needed and the reaction proceeded under ambient conditions in the reaction with formalin solution. The results strongly indicate that **Au:PVP** might possess superior catalytic activity toward the oxidation of hemiaminal intermediate when compared to other catalysts. Such characteristic features of **Au:PVP** will be applicable to many types of practical organic syntheses.

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References and Notes

1 a) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790. b) L. U. Nordstrøm, H. Vogt, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 17672. c) W.-J. Yoo, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 13064. d) S. Seo, T. J. Marks, *Org. Lett.* **2008**, *10*, 317. e) K. Shimizu, K. Ohshima, A. Satsuma, *Chem.—Eur. J.* **2009**, *15*, 9977.

2 H. Tumma, N. Nagaraju, K. V. Reddy, *J. Mol. Catal. A: Chem.* **2009**, *310*, 121.

3 T. Ishida, M. Haruta, *ChemSusChem* **2009**, *2*, 538.

4 B. Xu, L. Zhou, R. J. Madix, C. M. Friend, *Angew. Chem., Int. Ed.* **2010**, *49*, 394.

5 L. Zhou, C. G. Freyschlag, B. Xu, C. M. Friend, R. J. Madix, *Chem. Commun.* **2010**, *46*, 704.

6 a) J. J. Spivey, G. W. Roberts, M. C. Kung, C. K. Costello, H. H. Kung, *Catalysis* **2004**, *17*, 152. b) G. J. Hutchings, M. Haruta, *Appl. Catal., A* **2005**, *291*, 2. c) D. T. Thompson, *Top. Catal.* **2006**, *38*, 231. d) M. S. Chen, D. W. Goodman, *Catal. Today* **2006**, *111*, 22, and references therein.

7 a) H. Tsunoyama, H. Sakurai, Y. Negishi, T. Tsukuda, *J. Am. Chem. Soc.* **2005**, *127*, 9374. b) H. Tsunoyama, T. Tsukuda, H. Sakurai, *Chem. Lett.* **2007**, *36*, 212. c) H. Tsunoyama, H. Sakurai, T. Tsukuda, *Chem. Phys. Lett.* **2006**, *429*, 528. d) H. Tsunoyama, N. Ichikuni, H. Sakurai, T. Tsukuda, *J. Am. Chem. Soc.* **2009**, *131*, 7086.

8 H. Sakurai, H. Tsunoyama, T. Tsukuda, *Trans. Mater. Res. Soc. Jpn.* **2006**, *31*, 521.

9 a) H. Tsunoyama, H. Sakurai, N. Ichikuni, Y. Negishi, T. Tsukuda, *Langmuir* **2004**, *20*, 11293. b) H. Sakurai, H. Tsunoyama, T. Tsukuda, *J. Organomet. Chem.* **2007**, *692*, 368.

10 a) I. Kamiya, H. Tsunoyama, T. Tsukuda, H. Sakurai, *Chem. Lett.* **2007**, *36*, 646. b) H. Kitahara, I. Kamiya, H. Sakurai, *Chem. Lett.* **2009**, *38*, 908. c) H. Kitahara, H. Sakurai, *Chem. Lett.* **2010**, *39*, 46.

11 The variation of bases was studied and **2a** was obtained in moderate to excellent yield (61–94%). The % yield from different bases is showed here; 94% (KOH), 94% (NaOH), 93% ($LiCO_3$), 89% ($CsCO_3$), 83% (K_2CO_3), 79% ($Ca(OH)_2$), 61% ($KHCO_3$). Lower amounts of base diminished the reaction rate, while more than 200 mol % of base had no affect.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.