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ARTICLE

Chromium-Catalysed Efficient *N*-formylation of Amines with a Recyclable Polyoxometalate-supported Green Catalyst

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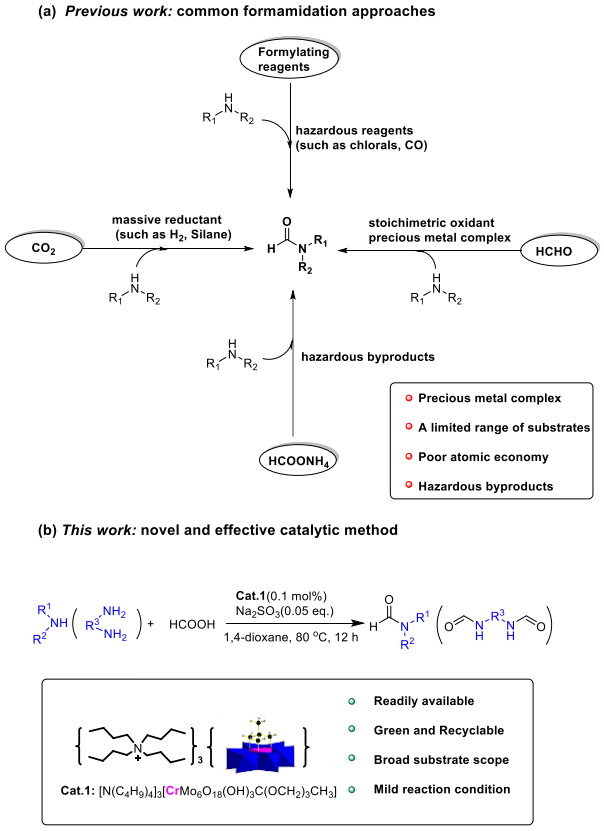
A simple and efficient protocol for the formylation of amines with formic acid, catalyzed by a polyoxometalate-based chromium catalyst, is described. Notably, this method shows excellent activity and chemoselectivity for the formylation of primary amines; diamines have also been successfully employed. Importantly, the chromium catalyst is potentially non-toxic, environmentally benign and safer than the widely used high valence chromium catalysts such as CrO_3 and $K_2Cr_2O_7$. The catalyst can be recycled several times with a negligible impact on activity. Finally, a plausible mechanism is provided based on the observation of intermediate and control experiments.

Introduction

The formamide group is an important functional group in the synthesis of pharmaceuticals and organic materials. [1-2] It is also a key chemical raw material for the production of bioactive molecules which possess high activity and reactivity in peptide synthesis. [3] The most common preparations of formamide compounds utilize formylating reagents, such as coupling reagents (e.g., DCC), [4] chloral, [5] carbon monoxide [6] and acetic anhydride, [7] to introduce the carbonyl moiety to construct the formamide bond [8] (Scheme 1). These procedures often rely on materials that are not commercially available and result in the generation of undesired waste products. Therefore, the development of an efficient and atom-economic method for the formation of formamide compounds is desirable. Recently, tremendous progress has been made in the use of some simple and readily available carbonyl-based starting materials, [9-11] such as ammonium formate, [9] methanol, [10] and carbon dioxide. [11] However, at present, these established methods all rely on utilizing complicated/commercially unavailable organic ligands, and harsh reaction conditions (such as high temperature and lengthy reaction time) (Scheme 1a). A more attractive method involves the use of formic acid as a coupling partner for formamide bond formation. This has the advantage of being inexpensive, using readily available compounds, and allows for functional group tolerance too. Until now, only a few examples of the *N*-formylation of primary and secondary amines with formic acid and its derivatives to *N*-formamides, catalyzed by noble metal catalysts (e.g. Pd, [12] Pt, [13] Au, [14] Rh, [15] etc.), have been reported. However, high costs and harsh reactions



Scheme 1. Comparison between previous and present work for the synthesis of formamides.

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conditions limit their industrial application, especially for the synthesis of biologically active compounds due to the toxicity of the noble metal catalysts. In light of the prevalence of inefficient catalytic methods available for the synthesis of formamides, there is a growing interest in the use of non-toxic and readily available catalysts.

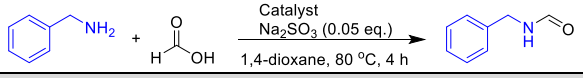
Polyoxometalates (POMs), a large class of metal–oxide clusters with oxidative redox and acidic properties, have received extensive attention in the field of organic synthesis. [16] As one of the types of POMs, the Anderson–Evans polyoxoanions exhibit good physical and chemical properties and are highly versatile, but they depend strongly on the heteroatom and few studies have been conducted regarding the counter-cation. Furthermore, Anderson POMs can be easily grafted because they possess six hydroxyl groups which provide unique catalytic properties. [17]

Spurred by our previous protocols [18] employed in the Cr-POM-catalyzed *N*-formylation of amines with methanol, herein, we report that a Cr-catalyst $[N(C_4H_9)_4]_3[CrMo_6O_{18}(OH)_3C(OCH_2)_3CH_3]$ (simplified as $Cr^{III}Mo_6$-CH_3) can efficiently catalyze the direct coupling of various primary and secondary amines with formic acid to afford the corresponding formamides with high catalytic activity and selectivity; the formylation of primary diamines has also been achieved (Scheme 1b). More importantly, the chromium catalyst is potentially non-toxic, environmentally benign and safer compared with widely used high valence chromium catalysts such as CrO_3 and K_2CrO_7. The catalyst can also be reused several times with the negligible loss of activity.

Results and discussion

Our study was initiated by examining formamide formation directly from benzylamine and formic acid in the presence of a catalyst and additive. We surprisingly found that compound **1** and Na_2SO_3 (0.05 equiv) were a suitable catalyst and additive for the reaction, giving the desired product in the best yield at 80 °C after 4 h reaction time (Table 1, entry 1). Interestingly, using $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$,

Table 1: Optimization of reaction conditions[a]



Entry	Cat.	Yield.(%)[f]
1	**1**	99
2	$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1.0)	42
3	$Cr(NO_3)_3{\cdot}9H_2O$	53
4	$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$+$Cr(NO_3)_3{\cdot}9H_2O$	73
5[b]	**1** (0.5)	76
6[c]	**1** (1.5)	86

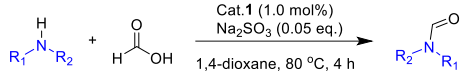
[a]Reaction conditions: Cat. **1** (1.0 mol%), benzylamine (1.0 mmol), formic acid (2.0 mmol), Na_2SO_3 (0.05 eq.), 1,4-dioxane (2.0 mL), stirring at 80 °C for 4 h. [b]Cat. **1** (0.5 mol%). [c]Cat. **1** (1.5 mol%). d Yields were determined by GC-MS analysis (internal standard is toluene).

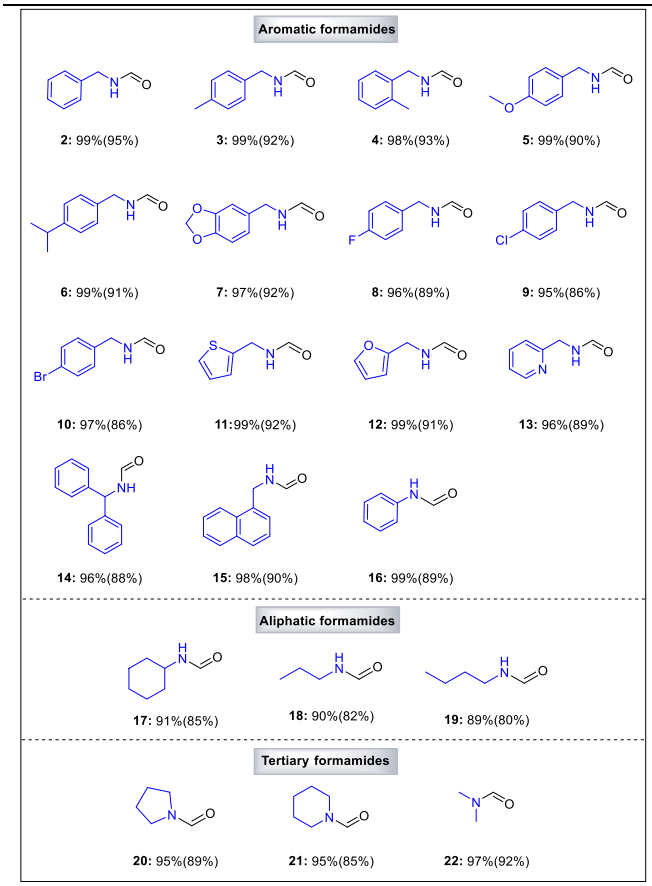
$Cr(NO_3)_3{\cdot}9H_2O$, or employing both together provided moderate catalytic activity (entry 2-4). Reducing the catalyst loading to 0.5 mol% resulted in a decrease in product yield. Increasing the catalyst loading to 1.5 mol% did not provide any substantial benefits to the reaction rate or efficiency (entry 5-6). (Full details are provided in the supplementary information and supplementary Table 1).

Finally, it was pleasing to see that the catalyst maintained its high activity over six reaction cycles. As confirmed by FT-IR spectroscopy, the recovered catalyst still retains the structural characteristics of Cat. **1** (Figures S1, S4-S5).

With the above optimized conditions in hand, we examined the direct formylation of various amine substrates with formic acid to determine the generality of the current procedure (Table 2). Benzylamine derivatives containing electron-rich aromatic amines underwent formylation giving the desired products in good to excellent isolated yields (3-7). Halogen-substituted aromatic amines, including F(8), Cl(9), Br(10), were also compatible with the catalyst, indicating the catalyst system possesses good catalytic performance

Table 2. *N*-formylation of amines using formic acids[a]





[a]Reaction conditions: Cat. **1** (1.0 mol%), amine (1.0 mmol), formic acid (2.0 mmol), 1,4-dioxane (2.0 mL), Na_2SO_3 (0.05 eq.), stirring at 80 °C for 4 h. [b]Yields were determined by ^{1}H-NMR, values in parentheses are the isolated yield.

and functional group tolerance. Additionally, primary amines containing electron-rich heterocyclic and oxidizable functionalities

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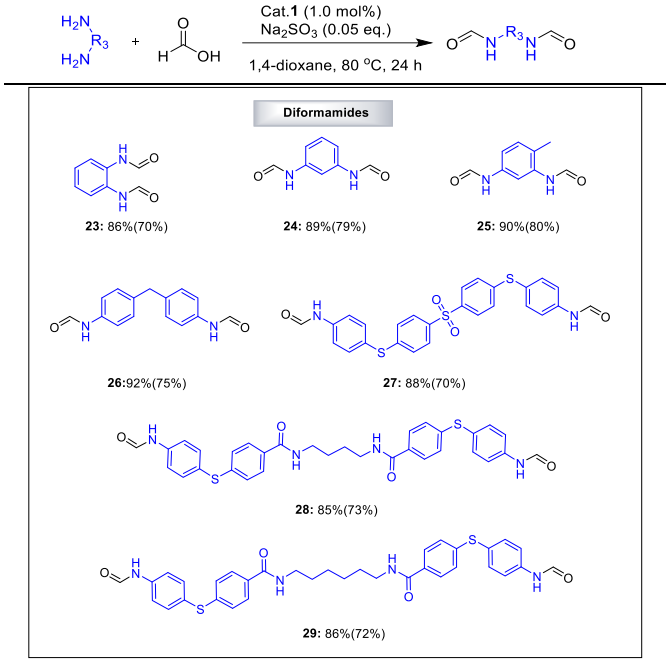
such as thiophene, furan and pyridine groups gave their corresponding formamides in 96-99 % yields due to their ability to coordinate with the metal active sites (11-13). Other aromatic amines incorporating sterically hindered groups (14-15) were also amenable to the reaction conditions. In addition, aniline derivatives (16) were also effective nucleophiles in the coupling reaction giving the corresponding formamides in excellent yields. Similarly, the scope of primary amines is not limited to benzylamines, with various branched aliphatic amines also being tolerated; cyclohexylamine (17), butylamine (18) and amylamine (19) afforded their corresponding formamides in good yields (89 %-91 %), with slight variation due to steric hindrance. We further examined the scope of this reaction by employing various secondary amines. To our delight, the corresponding formamide products, 1-formylpyrrolidine(20), *N*-formylpiperidine(21), *N*-ethylformamide (22), were obtained.

Table 3. *N*-formylation of diamines with formic acid [a,b]



[a]Reaction conditions: Cat. **1** (1.0 mol%), diamine (1.0 mmol), formic acid (4.0 mmol), Na_2SO_3 (0.05 eq.) stirring at a reaction tube at 80 °C for 24 h. [b]Yields were determined by ^{1}H-NMR, values in parentheses are the isolated yield.

Finally, due to the high functional group tolerance and reactivity of the present Cr-catalyzed *N*-formylation reaction of primary and secondary amines, a series of primary diamine studies were also carried out (Table 3). It is pleasing to note that the desired dimethylene amide derivatives were obtained in good yields (23-24). It is worth mentioning that commonly used chemical raw materials and intermediates, TDI and MDI, generated their desired formamide compounds 25 and 26 in 90 % and 92 % yields, respectively. Surprisingly, sulfur-containing diamines were also transformed into the corresponding diformamides in good yields (27-29). From the above substrate study, it can be seen that our methodology is highly chemoselective and that the catalytic system could play a pivotal role in future formamide couplings of amines with formic acid. Finally, a gram-scale reaction was conducted with 1.0 mol% of catalyst, 2.14 grams (20.0 mmol) benzylamine and formic acid (40.0 mmol) in 5.0 mL 1,4-dioxane. Analytically pure formamide was isolated in 96% yield after 4 hours (Figure 1).

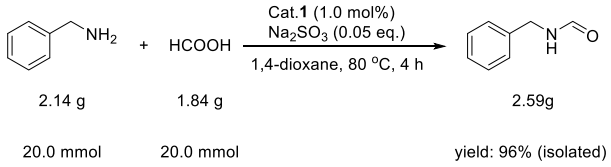


Figure 1: Gram-scale reaction.

To gain insight into the mechanism, some control experiments involving the formylation of benzylamine with formic acid were conducted. When only Na_2SO_3 was employed stoichiometrically, none of the formamide product was detected after mixing with formic acid, indicating that Na_2SO_3 is not an activating reagent (Figure 1a(1)). On the contrary, the addition of $Cr^{III}Mo_6$-CH_3 gave the desired benzamide in 35 % yield (Figure 1a(2)), which indicates the

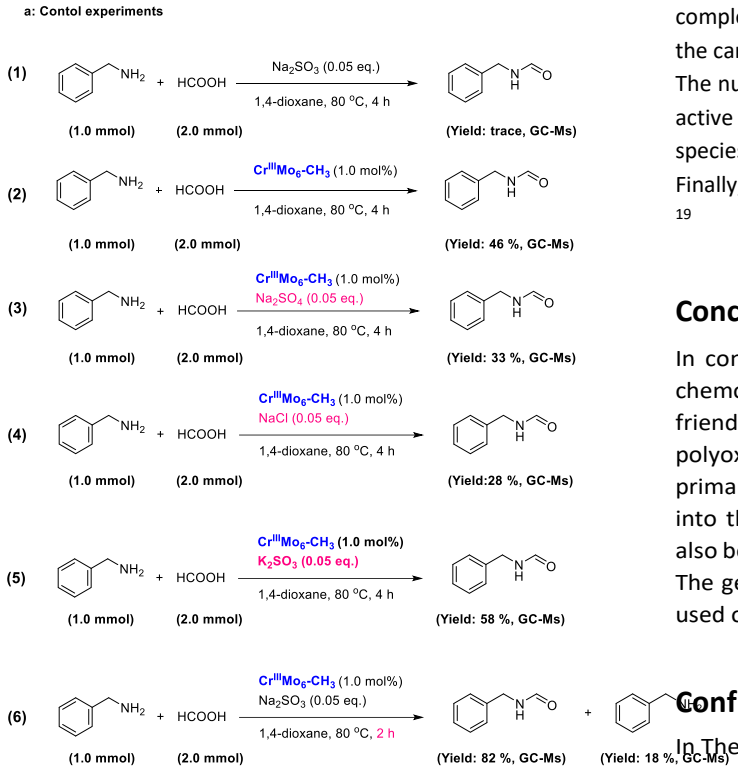


Figure 2: Control experiments and a plausible mechanism

complexation of the $Cr^{III}Mo_6$-CH_3 catalyst with formic acid generates new reactive substances. Changing the additive from Na_2SO_3 to Na_2SO_4, NaCl and K_2SO_3 had a significant influence on product yield. This is most likely because the SO_3^{2-} anion greatly increases the efficiency of electron transfer [18] (Figure 2a (3-5)). When the reaction was stopped after 2 h, the product and benzylamine were both detected in 82 % and 18 % yield, respectively, suggesting that a certain amount of the benzylamine attacks the carbonyl group of the reactive intermediate to produce a formamide product (Figure 2a (6)).

Based on the above experimental results, a mechanism is proposed as shown in Fig. 1. This mechanism involves the complexation of catalyst **1** with formic acid. The Cr catalyst activates the carbonyl group of formic acid to form the covalent compound A. The nucleophilic amines attack the carbonyl carbon of A to give the active intermediate B. After N-H bond heterolysis, highly reactive species C, which can be regard as active self-dehydrating agent. Finally, the elimination of water from C gives the formamide product. [19]

Conclusions

In conclusion, we have demonstrated a simple, efficient and chemoselective one-pot strategy for the environmentally friendly formylation of amines with formic acid using a polyoxometalate-based Cr-catalyst ($Cr^{III}Mo_6$-CH_3). A number of primary and secondary amines can be successfully converted into the corresponding formamide products. The catalyst can also be recycled several times with the negligible loss of activity. The generality of this methodology gives it the potential to be used on an industrial scale.

Conflicts of interest

In There are no conflicts to declare.

Acknowledgements

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