Organic LETTERS

Letter

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Nickel-(II)-Catalyzed *N*-Formylation and *N*-Acylation of Amines

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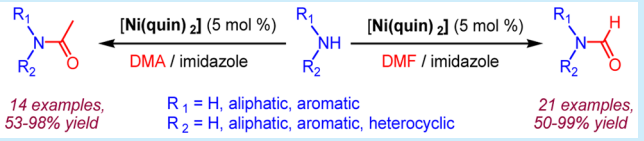
Supporting Information

ABSTRACT: A highly efficient protocol of Ni(II) metal complex, [Ni(quin)$_2$], catalyzing *N*-formylation and *N*-acylation of amines with moderate to excellent yields, using *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide in the presence of imidazole, is described here. The protocol shows broad substrate scope for aliphatic, aromatic, and heterocyclic amines.



N-Formylation and amidation of amines are very useful reactions in synthetic organic chemistry.[1−3] Furthermore, the amide bond is usually present in drug molecules, materials, agrochemicals, and other natural products.[4] Some of the representative and important drugs such as vildagliptin, lacosamide, paracetamol, chloramphenicol, formoterol, captopril, atorvastatin, enalapril, lidocaine, and many others also have amide bonds (Figure 1).

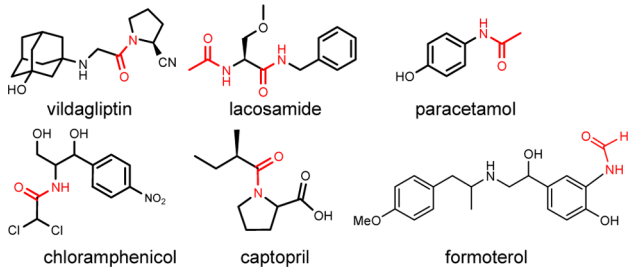


Figure 1. Amide bonds in some drug molecules.

N,*N*-Dimethylformamide (DMF) is primarily used as a polar solvent in chemical reactions. As a formamide containing an aldehyde and amino group, DMF can serve as a precursor to generate a wide range of intermediates in organic reactions, including −CONMe$_2$, CHO, −NMe$_2$, −CO, −Me, etc.[5] Numerous methods are available for *N*-formylation and *N*-acylation of amines with various carbonyl sources such as formic acid,[6] formate,[7] *N*,*N*-dimethylformamide,[8] *N*,*N*-dimethylacetamide,[8] esters,[9] and methanol.[10]

Several metals and metal complexes have been reported for reaction reactions, such as copper,[11] Fe(III),[12] [Pd(OAc)$_2$],[13] ZnCl$_2$ and other Lewis acids,[14] ZnO,[15] carbon nanotube−gold nanohybrid (Au−CNT),[16] indium,[17] nanocerium oxide,[18] K$_3$PO$_4$,[19] heteropolyanion-based ionic liquids (HPAILS),[20] *o*-aryl oxide−*N*-heterocyclic carbene ruthenium(II) ([Ru−NHC] complex),[21] molybdate sulfuric acid,[22] H$_2$SO$_4$SiO$_2$,[23] sulfated tungstate catalyst,[24] and many others.[25] However, a number of these methods suffer from drawbacks such as the use of expensive toxic formylating agents, use of costly catalysts, formation of byproducts, and critical workup processes, and a few of them are time-consuming.

Recently, Hudson et al.[26] developed a protocol for the N-formylation of amino acid esters and primary amines using imidazole in warm DMF. However, it failed with aromatic and secondary amines. Nickel-catalyzed reactions have gained considerable attention because of their low cost, quick availability, high reactivity, and unique properties including nontoxicity and inertness toward air and water.[27,28]

As part of our research efforts to develop new synthetic methods using nickel, it was found that the Ni(II)−metal complex with 8-hydroxyquinoline as bidentate ligand and [Ni(quin)$_2$] catalyst **C1** (Figure 2) can carry out the *N*-formylation and *N*-acylation of amines under nonstringent conditions conveniently.

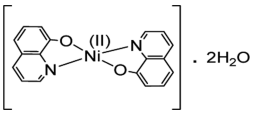
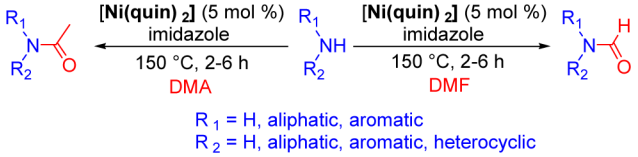


Figure 2. [Ni(quin)$_2$] catalyst **C1**.

Herein, we report a highly efficient protocol of [Ni(quin)$_2$]-catalyzed *N*-formylation and *N*-acylation of amines using DMF and *N*,*N*-dimethylacetamide (DMA) in homogeneous medium (Scheme 1).

Scheme 1. *N*-Formylation and *N*-Acylation of Amines Using [Ni(quin)$_2$]



Received: March 7, 2017

DOI: 10.1021/acs.orglett.7b00660
Org. Lett. XXXX, XXX, XXX−XXX

The protocol shows broad substrate scopes for aliphatic, aromatic, and heterocyclic amines with moderate to excellent yields in the presence of 5 mol % of [Ni(quin)$_2$] and imidazole as base at a temperature of 150 °C. The reagents and catalyst used are cheaper and do not require inert atmosphere. Furthermore, an additional advantage is the reaction workup, which involves wash of organic layer with hydrochloric acid solution (1 M) avoids further purification techniques like column and flash chromatography or crystallization. The corresponding *N*-formylated and *N*-acylated products are isolated with moderate to excellent yields (50−99%).

In preliminary reactions, 2,4-dimethylaniline (**1a**) was treated with 2.5 mL of DMF in the presence of 5 mol % of [Ni(quin)$_2$] and 3 equiv of weak organic bases like triethylamine, DABCO, and 2,6-lutidine at 150 °C for 24 h, with resulting yields of formamide up to 25−28% (Table 1, entries 1−3). Subsequently, the use of inorganic bases like CH_3COONa, *t*-BuOK, CH_3ONa, and NaH showed some undesired spots on TLC and a yield of formamide up to 35−65% (Table 1, entries 4−7). In the case of strong inorganic bases NaOMe and NaH, vigorous exotherm with tar formation was observed.

When a reaction was carried with 5 mol % of catalyst and DMF (5 mL) with 3 equiv of imidazole, moderate yield (68%) was seen at a temperature of 150 °C (Table 1, entry 8). A control experiment, without catalyst and with 2.5 mL of DMF and 3 equiv of imidazole, was found to give lower yields (about 6%, Table 1, entry 9). When 1 mol % of catalyst at 150 °C was used, an improvement in yield up to 20% was observed (Table 1, entry 10). An imidazole acting as a base as well as an acyl-transfer agent,[26] not as substrate, was proved by the following experiment: when the reaction was carried out in the absence of substrate, *N*-formylated product of imidazole was confirmed by TLC, without aqueous workup (not isolated as this is highly reactive toward water) (Table 1, entry 11). When the reaction was performed with a catalytic amount of copper powder and [$NiCl_2$·$6H_2O$] instead of [Ni(quin)$_2$], a lower conversion and isolated yield (about 6% each) were obtained (Table 1, entries 12 and 13), suggesting the [Ni(quin)$_2$] complex may be responsible for the activation of DMF and can carry out *N*-formylation efficiently. In order to investigate the effect of the solvents, reactions were carried out in *o*-xylene and 1,4-dioxane, where no conversion was seen (Table 1, entries 14 and 15). During optimization attempts, the reaction was performed at lower temperatures, i.e., ambient temperature 50 and 80 °C, and no conversion of product was found (Table 1, entry 16), while at 120 °C a higher yield (40%) was seen (Table 1, entry17).

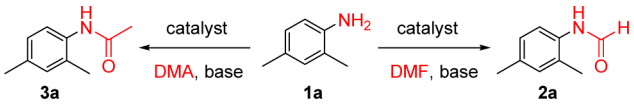
Finally, the reaction was found to be efficient with 5 and 10 mol % of catalyst in 2.5 mL of DMF and 3 equiv of imidazole at 150 °C, affording a yield of the product with 96% each within 2 h (Table 1, entries 18 and 19). While exploring a method for *N*-acylation, a separate experiment was performed on 2,4-dimethylaniline (**1a**) using DMA instead of DMF at optimized conditions without any other solvent; an excellent isolated yield up to 95% was seen within 2 h.

Once optimized, *N*-formylation and *N*-acylation using DMF and DMA were successfully carried out for different aromatic, aliphatic, and heterocyclic amines. It was observed that different functionalities on anilines such as hydroxy, alkyl, nitro, and halogens were unaltered (Scheme 2, 3). Anilines containing electron-donating groups like alkyl and -OMe underwent the conversion smoothly with excellent yields **2a**−**e**, while electron-withdrawing groups like −NO_2 and −COOH at the *ortho* and *para* positions did not show any conversion and at the *meta* position gave a lower yield of **2f**. For halide-substituted anilines, better conversions were seen at both the *meta* and *para* positions (**2g**−**i**,**k**−**n**), while for chlorine at the *ortho* position lower yields were obtained (**2j**). 2-(Trifluoromethyl)-6-methylbenzenamine, 2,6-dichloroaniline, 2,3-dichloroaniline, 2,6-dimethoxyaniline, and 2,6-dimethylaniline did not show any conversion. This can be attributed to the size of the substituent at the *ortho* position that exhibits steric hindrance, resulting in lower conversion. Excellent yields were seen with other primary aliphatic amines **2o**−**r**.

After successful *N*-formylation of primary aromatic amines, the protocol was tested for secondary and heterocyclic amines and was found to be as efficient as for primary amines **2s**−**u**. A couple of exceptions for secondary amines like *N*,*N*-diphenylamine and *N*,*N*-dicyclohexylamine did not show any conversion, which may be due to the decrease in nucleophilicity and steric hindrance, respectively. This reactivity was further tested for O-formylation of phenols but was found to be unsuccessful.

The strategy was further extrapolated for *N*-acylation of various aliphatic, aromatic, and heterocyclic amines using DMA as acylating source in the presence of [Ni(quin)$_2$] that gave

Table 1. Selected Observations during Reaction Optimization[a]



no.	catalyst (mol %)	base (equiv)	solvent (mL)	**2a** yield[b] (%)
1	**C1** (5)	TEA (3)	DMF (2.5)	25
2	**C1** (5)	DABCO (3)	DMF (2.5)	25
3	**C1** (5)	2,6-lutidine (2)	DMF (2.5)	28
4	**C1** (5)	$NaOCOCH_3$ (3)	DMF (2.5)	35
5	**C1** (5)	KOtBu (2)	DMF (2.5)	55
6	**C1** (5)	NaOMe (5)	DMF (2.5)	60
7[c,d]	**C1** (5)	NaH (1.5)	THF (2.5)	65
8	**C1** (5)	imidazole (3)	DMF (5)	68
9	**C1** (0)	imidazole (3)	DMF (2.5)	6
10	**C1** (1)	imidazole (3)	DMF (2.5)	20
11[e]	**C1** (5)	imidazole (1)	DMF (2.5)	nil[k]
12[f]	**C2** (5)	imidazole (3)	DMF (2.5)	6
13[g]	**C3** (5)	imidazole (3)	DMF (2.5)	6
14[d]	**C1** (5)	imidazole (3)	o-xylene (2.5)	nil
15[d]	**C1** (5)	imidazole (3)	1,4-dioxane (2.5)	nil
16[h]	**C1** (5)	imidazole (3)	DMF (2.5)	nil
17[i]	**C1** (5)	imidazole (3)	DMF (2.5)	40
18[j]	**C1** (5)	imidazole (3)	DMF (2.5)	96
19[j]	**C1** (10)	imidazole (3)	DMF (2.5)	96

[a]All reactions were carried out on approximately a 0.5 g scale using 2,4-dimethylaniline (**1a**) (4.13 mmol, 1 equiv), solvent (2.5 mL, 5 volume), [Ni(quin)$_2$] (**C1**) 1−10 mol %, base (1−5 equiv), temperature 150 °C for 24 h. All reagent and substrate addition was done at room temperature (25 °C). [b]Isolated yields. [c]Reaction temperature at 70 °C. [d]DMF (2 equiv). [e]Reaction carried out without **1a**. [f]Cu powder catalyst (**C2**). [g][$NiCl_2$·$6H_2O$] catalyst (**C3**). [h]Reaction temperature initially at ambient temperature then increased up to 50 and 80 °C. [i]Reaction temperature at 120 °C. [j]Reaction continued up to 2 h. [k]Not isolated; a product formed, i.e., *N*-formylimidazole is highly reactive toward water.

DOI: 10.1021/acs.orglett.7b00660
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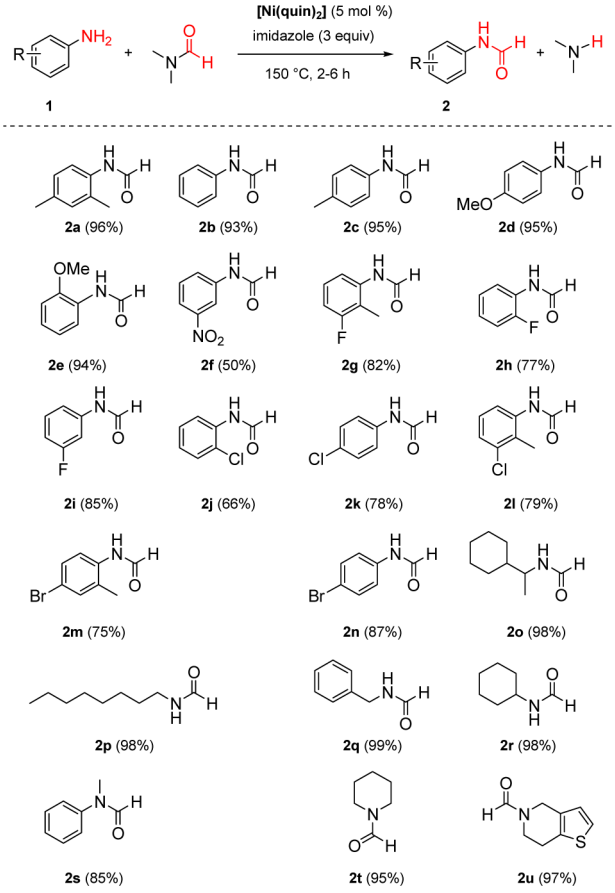
Scheme 2. Scope of *N*-Formylation of Amines Using [Ni(quin)$_2$] and DMF[a]



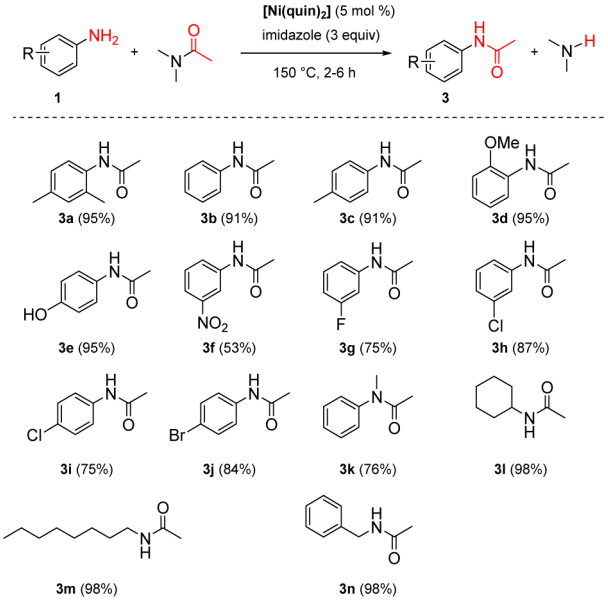
[a]Reaction conditions: **1** (0.5 g, 1 equiv), [Ni(quin)$_2$] (5 mol %), imidazole (3 equiv), in DMF (2.5 mL, 5 volume), temperature 150 °C for 2−6 h. Isolated yields are given.

moderate to excellent yields (Scheme 3). These reactions also experienced similar effects on conversion for the compounds with substituents having electron-donating/withdrawing groups and steric hindrance on *ortho*, *meta*, and *para* positions.

A plausible mechanism for the *N*-formylation of amines, in accordance with the results of our experiments, is represented in Scheme 4. Initially, DMF is activated via coordination with [Ni(quin)$_2$] (similar to activation with Lewis acid[14]). Nucleophilic attack of imidazole on activated DMF results in the formation of a tetrahedral intermediate **A**. Breakdown of intermediate **A** leads to the formation of reactive *N*-formylimidazole (intermediate **B**) with evolution of dimethyl amine gas. Intermediate **B** acts as an acyl-transfer reagent for the *N*-formylation of amines. Nucleophilic attack of the amine on intermediate **B** gives a tetrahedral intermediate **C** followed by extrusion of imidazole that results in the formation of intermediate **D**. Finally, intermediate **D** furnishes *N*-formylated product, recycling the [Ni(quin)$_2$].

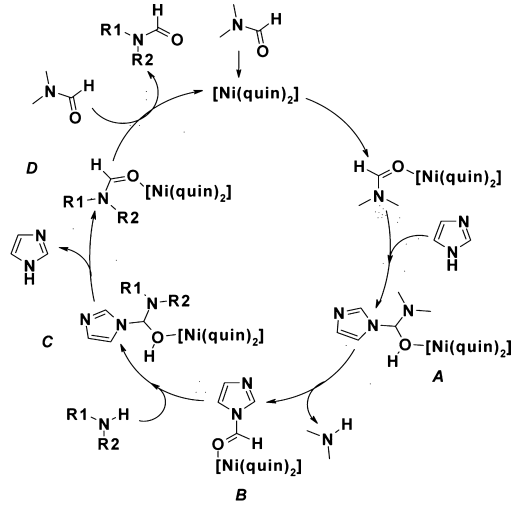
Although a complete revelation of the mechanism has not been assumed, a few controlled experiments were conducted to define the specific role of catalyst and precise nature of the intermediates for these novel transamidation reactions. During experiments with optimized conditions, the evolution of a gas having typical amine smell was noticed. Hence, an experiment was performed with **1a**, where this evolved gas was trapped in chilled water. Characterization of trapped water solution by

Scheme 3. Scope of *N*-Acylation of Amines Using [Ni(quin)$_2$] and DMA[a]



[a]Reaction conditions: **1** (0.5 g, 1 equiv), [Ni(quin)$_2$] (5 mol %), imidazole (3 equiv), in DMA (2.5 mL, 5 volume), temperature 150 °C for 2−6 h. Isolated yields are given.

Scheme 4. Plausible Mechanism for *N*-Formylation Using [Ni(quin)$_2$]



GCMS proved that the evolved gas is none other than *N*,*N*-dimethylamine supporting the DMF as formyl (CHO) source. An experiment was performed with **1a**, where, instead of DMF, *N*-formylimidazole was used as a formyl source and THF as a solvent at ambient temperature with vigorous stirring for 24 h in which an excellent isolated yield of *N*-formylated product up to 92% was seen. This supports the mechanism where the reactive *N*-formylimidazole (intermediate **B**) act as an *N*-acyl-transfer agent. The data provide several revelations regarding the identity of this plausible mechanism. Pleasantly, all of the *N*-formylation reactions proceeded efficiently and furnished all types of substituted amines, and subsequently this mechanism also worked for *N*-acylation of substituted amines using DMA as acylating source with moderate to excellent yields.

DOI: 10.1021/acs.orglett.7b00660
Org. Lett. XXXX, XXX, XXX−XXX

In conclusion, a highly efficient protocol using [Ni(quin)$_2$] has been developed with imidazole as homogeneous medium for *N*-formylation and *N*-acylation of aliphatic, aromatic, and heterocyclic amines. The advantages of the present protocol are moderate to excellent yields, no requirement of inert atmosphere, easy workup, and purification procedures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00660.

Experimental procedures, characterization of compounds **2a−u**, **3a−n**, and catalyst [Ni(quin)$_2$] (^{1}H and ^{13}C NMR spectra), optimization table, and X-ray diffraction data for ligand (8-hydroxyquinoline), catalyst [Ni(quin)$_2$], and [$NiCl_2 \cdot 6H_2O$] (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Baburaoji Gholap Research Center for support.

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DOI: 10.1021/acs.orglett.7b00660
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