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# Research paper

*N*-Formylation of amines using arylhydrazones of malononitrile and a Cu(II) complex under eco-friendly conditions at room temperature

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# N-Formylation of amines using arylhydrazones of malononitrile and a

# Cu(II) complex under eco-friendly conditions at room temperature

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#### ABSTRACT

In this work, we report the synthesis of formamides via solvent free N-formylation of amines arylhydrazones malononitrile using known of including sodium 2-(2-(dicyanomethylene)hydrazinyl)benzenesulfonate (I), 2-(2-(dicyanomethylene)hydrazinyl) benzoic acid (II) and its Cu(II) complex (III) as catalysts at room temperature. These catalysts are highly active and the scope of the method was investigated using several heterocyclic, aromatic and aliphatic amines as substrates, which produced the corresponding formamides in high yields. The remarkable advantages of this method are the elimination of toxic solvents, operational simplicity, easy workup procedure, excellent yields and avoidance of column chromatography.

*Keywords: N*-Formylation; Amines; Formamides; Solvent-Free; Copper; Arylhydrazones of malononitrile

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#### 1. Introduction

Formamides as a very important class of amine derivatives have attracted the attention of many chemists and pharmacists due to their extensive range of applications in diverse areas of sciences and industries from synthetic organic chemistry to large-scale production [1]. They have been widely used as intermediates in the preparation of various pharmaceutical compounds, especially cancer chemotherapeutic agents [1]. Moreover, formamides are employed for the protection of the nitrogen of amines and in the production of isocyanides and formamidines [2,3]. Formamides can also act as Lewis base catalysts in the hydrosilylation of carbonyl compounds, preparation of acid chlorides and allylation [4,5].

Owing to the wide applications of formamides, the development of novel methods for their preparation using formylation reagents has attracted considerable interest [6-10]. Many processes have been studied for the formamide preparation by different reagents such as chloral [11], acetic formic anhydride [12], activated formic acid by N,N'-dicyclohexylcarbodiimide (DCC) [13], 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) [14] activated formic esters [15,16], NH<sub>4</sub>HCO<sub>2</sub> [17], polyethylene glycol 400 (PEG-400) [18] and 2,2,2-trifluoroethyl formate [19].

The different methods reported for the synthesis of formamides suffer from certain drawbacks, such as harsh reaction conditions, low yields, use of toxic and expensive formylating reagents and expensive homogeneous and heterogeneous catalysts, and formation of by-products. Thus, there is still a high demand to improve the common synthetic methods, namely by reducing or avoiding the use of hazardous and expensive compounds.

Among the important formylating agents, HCOOH has been widely investigated and it mostly displayed efficient ability in the *N*-formylation of amines because of its low-cost, and accessibility from biomass-derived renewable materials [6].

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In recent years, the common approaches for the preparation of formamides have been based on the *N*-formylation of amines using HCOOH as a common formylating agent and a variety of catalysts such as transition metal/metal oxide catalysts (NiO, ZnO, *etc.*), inorganic solid oxides (zeolite, silica gel, alumina, *etc.*) and acidic catalysts (AlCl<sub>3</sub>, ZnCl<sub>2</sub>, NiCl<sub>2</sub>, *etc.*) [6]. However, the use of most of these catalysts has several disadvantages, such as high cost, harsh synthetic procedures, tedious work-up, low yields, and the utilization of moisture sensitive and toxic/expensive reagents. Thus, it is desirable to develop more convenient methods for the production of formamides, namely by using organocatalysts or their metal complexes under simple conditions and in the absence of toxic and expensive solvents or reagents.

We have reported [20,21] the synthesis in good yields of arylhydrazones of malononitrile, such as (I) and (II), and of a copper complex (III) bearing II (in basic form) as ligand (Scheme 1).



Scheme 1. Schematic representations of I – III [20,21].

In the present work and in continuation of our studies on the preparation of various aroylhydrazone catalysts and their application in organic synthesis [22-26], we have focused

on the synthesis of formamides in high yields *via N*-formylation of various amines with HCOOH (formic acid) under mild conditions using the organo compounds (I) and (II), or the Cu(II) complex (III) as catalysts (Scheme 2).



Scheme 2. Preparation of formamides using catalysts I, II or III.

#### 2. Experimental

#### 2.1. Tools and reagents

All chemicals used in this study were obtained from Merck/Sigma Aldrich Chemical Co. and directly used as received without further purification. FTIR spectra were recorded using a Perkin Elmer 781 spectrophotometer by mixing the samples with KBr, pressing into pellets, and scanning from 4000 to 400 cm<sup>-1</sup>. The NMR spectra were recorded using a Bruker Avance DRX-300 MHz instrument. An electrothermal 9100 apparatus was applied for measuring the melting points.

# 2.2. Preparation of arylhydrazones of malononitrile (I and II)

The synthesis and characterization of compounds (I) and (II) were carried out according to our previous work [20,21].

#### 2.3. Preparation of copper(II) complex (III)

Green crystals of complex (III) were prepared according to our reported work by reacting compound (II) with  $Cu(CH_3COO)_2 \cdot H_2O$  in methanol under reflux conditions for 0.5 h [21].

# 2.4. General experimental procedure for the preparation of formamides

A mixture of amine (0.5 mmol), HCOOH (99%, 1 mmol) and catalyst (typically 0.030 g, *i.e.*, 0.12, 0.14 or 0.024 mmol of catalyst I – III, respectively) was stirred at room temperature for

appropriate time. Upon completion of the reaction (followed by TLC), the reaction mixture was washed with water and then treated with EtOAc to separate the pure product. The FTIR and NMR spectral data were found to be identical with those reported in our previous works [7-10].

*N-(2-Hydroxyphenyl) formamide* 

M.p. 130-131 °C (lit. 129-131°C [27])

FT-IR (KBr, cm<sup>-1</sup>) 3376, 3104, 1656, 1591, 1535, 1453, 1378, 1280, 1251, 1206, 1098, 751, 664.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\rm H}$  8.29 (d, 1 H, J = 2.0 Hz), 8.16 (brs, 1H), 7.61 (brs, 1H), 7.22 (dd, 1H, J = 8.0 Hz, J = 1.4 Hz), 7.17 (t, 1H, J = 8.6 Hz), 7.04 (dd, 1H, J = 8.0 Hz, J = 1.4 Hz), 6.92 (t, 1H, J = 8.4 Hz).

# 3. Results and discussion

The compounds (I), (II) and (III) were prepared and characterized according to our previous work [20,21], and their catalytic potential was assessed in the synthesis of formamides by N-formylation of amines with formic acid (Scheme 2).

2-Chlorophenylamine was selected as the model substrate and the copper complex III as the catalyst. To determine the optimum reaction conditions, the effects of different parameters, such as the amounts of complex (III) and HCOOH, were studied. The results are summarized in Table 1. Initially, the reaction was attempted in the absence of complex (III) but it did not proceed and no products were formed even after 5 h at room temperature (Table 1, entry 1). Subsequently, to establish the importance of complex (III) and HCOOH in the formation of N-(2-chlorophenyl) formamide, different amounts of these compounds were used. The best result was obtained using 0.024 mmol (0.030 g) of complex (III) in the

presence of HCOOH (1.0 mmol) as the formylating agent at room temperature (Table 1, entry 5). The reaction was performed at ambient temperature in the presence of compounds (I) and (II), with achieved product yield of 91 and 92% after 70 min of reaction time, respectively (Table 1, entries 6 and 7). Next, the same reaction was carried out with various copper catalyst salts, such as  $Cu(CH_3COO)_2$ ·H<sub>2</sub>O and  $Cu(NO_3)_2$ ·2.5H<sub>2</sub>O, which generated lower product yields (Table 1, entries 8 and 9).

 Table 1. Solvent-free N-formylation of 2-chlorophenylamine (0.5 mmol) with HCOOH (99%) catalysed by III

 under different conditions at ambient temperature. <sup>a</sup>

Entry	HCOOH (mmol)	III (mmol)	Time	Yield % <sup>a</sup>	TON <sup>c</sup>
1	1.0	<b>III</b> (0)	5 h	0	0
2	0.5	<b>III</b> (0.016)	120 min <sup>b</sup>	74	23.1
3	0.5	III (0.024)	120 min <sup>b</sup>	80	16.7
4	0.5	<b>III</b> (0.033)	120 min <sup>b</sup>	85	12.9
5	1.0	<b>III</b> (0.024)	60 min	95	19.8
6	1.0	I (0.12)	70 min	91	3.8
7	1.0	<b>II</b> (0.14)	70 min	92	3.3
8	1.0	Cu(CH <sub>3</sub> COO) <sub>2</sub> ·H <sub>2</sub> O (0.024)	165 min <sup>b</sup>	70	15
9	1.0	Cu(NO <sub>3</sub> ) <sub>2</sub> ·2.5H <sub>2</sub> O (0.024)	135 min	82	17

<sup>a</sup>Yields are after work-up. <sup>b</sup>Not complete. <sup>c</sup>Turnover number (number of moles of product per mole of catalyst); divide by 4 in order to obtain the value per mole of Cu (or per mole of ligand).

After the determination of the optimal reaction conditions, a range of substrates was evaluated. The added solvent free reactions of various amines (aromatic, heterocyclic and aliphatic) with HCOOH were carried out using catalysts (I), (II) and (III) at room temperature. A wide variety of primary and secondary amines containing electron donating and withdrawing substituents was converted to the corresponding formamides in high yields and the results are shown in Table 2. According to the results obtained, column chromatography or recrystallization are not required for the purification.

#### Table 2

*N*-Formylation of amines (0.5 mmol) with HCOOH (1.0 mmol) using 0.030 g of catalyst (0.12, 0.14 or 0.024 mmol of **I**, **II** or **III**, respectively), at different reaction times.

Entry	Amine	Product	Catalyst	Time (min)	Yield % <sup>a</sup>	TON <sup>b</sup>
1	NH <sub>2</sub>		I II III	70 70 60	90 91 92	3.8 3.3 19.2
2	Me NH <sub>2</sub>	Me NHCHO	I II III	60 60 50	92 92 93	3.8 3.3 19.4
3	MeO-NH <sub>2</sub>	MeO-NHCHO	III	40	94	19.6
4	Cl NH2	Cl NHCHO	I II III	70 70 60	91 92 95	3.8 3.3 19.8
5	Br-NH2	Br————————————————————————————————————	I II III	55 55 50	92 90 93	3.8 3.2 19.4
6	OH	OH OH	ш	85	92	19.2
7	NHMe	NCHO(Me)	III	75	80	16.7
8	CH <sub>2</sub> NH <sub>2</sub>	СН2NHCHO	I II III	70 70 60	88 86 88	3.7 3.1 18.3
9	ONH	О мсно	III	65	89	18.5

<sup>a</sup>Yields are after work-up. <sup>b</sup>Turnover number (number of moles of product per mole of catalyst); divide by 4 in order to obtain the value per mole of Cu (or per mole of ligand).

The role of catalysts (I), (II) and (III) in the synthesis of formamides can be accounted for by the proposed mechanism in Scheme 3. The catalyst acidic sites (Bronsted and Lewis acids) present in the acid reaction medium can activate the carbonyl group of HCOOH *via* interaction with its oxygen atom [6,28]. This enhances the electrophilic character of the carbon atom of the carbonyl, making it more vulnerable to the nucleophilic attack by the nitrogen of amines. This attack on the activated carbonyl group converts the amine into the corresponding formamide.



Scheme 3. Proposed mechanism for the preparation of formamides using catalysts (I), (II) and (III).

The desired formamides were characterized by CHN, melting points, FTIR and NMR [7-10]. The disappearance of the strong absorption band (NH<sub>2</sub> stretching band) in the FTIR spectrum of the amine and the appearance the one absorption band due to the carbonyl stretching (*N*-formyl, C=O) in the range of 1640-1690 cm<sup>-1</sup> confirmed the formation of the formamides (Figures S1, S2 and S4). The FTIR spectra also showed a signal around 3200-3400 cm<sup>-1</sup>, corresponding to the secondary NH stretching vibrations. However, this signal was not observed in the FTIR spectra of the formamides from secondary amines such as *N*-methylaniline (Figure S4). The <sup>1</sup>H NMR spectra of the *N*-formamides showed the expected two signals for the NH and aldehyde protons (Figure S3).

# 4. Conclusions

In summary, we have developed a solvent free synthetic method for the synthesis of formamides at room temperature using arylhydrazones of malononitrile (I and II) and Cu(II) complex (III) as effective catalysts. The catalysts used in the synthesis of formamides showed good catalytic activity and the products were formed in good to excellent yields. Using compounds (I) and (II) as catalysts, relatively similar performances with respect to

reaction time and yield for the preparation of formamides were obtained. In contrast with compounds (I) and (II), the higher yield and lower reaction time can be seen in the synthesis of formamides with the Cu(II) complex (III). However, the presence of copper (in the tetranuclear catalyst III) does not improve considerably the process in terms of turnover number per mole of copper (or of ligand). The present method has various advantages including simple operation, mild reaction conditions, high yields, low catalyst load, and no need for product purification. Further investigations on the application of these catalysts in organic synthesis are in progress.

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# Highlights:

- > *N*-Formylation of amines using arylhydrazones of malononitrile.
- > The reaction can be performed under solvent-free conditions at room temperature.
- > The products were obtained in excellent yields without of column chromatography.

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All persons who have made substantial contributions to the work reported in the manuscript (e.g., technical help, writing and editing assistance, general support), but who do not meet the criteria for authorship, are named in the Acknowledgements and have given us their written permission to be named. If we have not included an Acknowledgements, then that indicates that we have not received substantial contributions from non-authors.

Best regards, Mahmoud Nasrollahzadeh (on behalf of all the co-authors)

مارز Graphical Abstract

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