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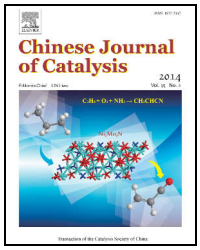

Article

Highly efficient and clean synthesis of 1-amino-2-acetylanthraquinone by copper-catalyzed reductive cleavage of isoxazole motif

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ABSTRACT

A clean and highly efficient synthesis of 1-amino-2-acetylanthraquinone via reductive isoxazole ring cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione catalyzed by trace copper using hydrazine hydrate as a clean reducing agent and water as a green reaction medium under mild reaction conditions was investigated. Various transition-metal catalysts were screened for the reductive ring-opening reaction, and $Cu(NO_3)_2$ was shown to be an excellent catalyst. A conversion of 97.2% and 1-amino-2-acetylanthraquinone selectivity greater than 95% were obtained in the presence of 2.6 mol% $Cu(NO_3)_2$ (turnover number 38) with 1.3 equiv. of hydrazine hydrate for 2 h in water. The structure of the product was confirmed by ^1H nuclear magnetic resonance spectroscopy and mass spectrometry; the main byproduct was hydroxyl-substituted 1-amino-2-acetylanthraquinone. A possible reaction mechanism for the copper-catalyzed ring cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione with hydrazine hydrate was proposed.

1. Introduction

Many natural or artificial dyes and fine chemicals contain the isoxazole motif [1–4] and its ring cleavage is an important reaction. It has gained much attention in the dye/pigment and other chemical industries because isoxazole cleavage can produce a series of useful *ortho*-amino ketones, which are important organic intermediates in the dye, pigment, medical, and petrochemical fields [5–7]. 1-Amino-2-acetylanthraquinone is an *ortho*-amino ketone, and it is a key intermediate in the production of dyes and pigments such as Vat blue 66 [8].

Significant efforts have been made to achieve reductive cleavage of isoxazoles for the efficient synthesis of *ortho*-amino ketones, and this is considered to be one of the "Holy Grails" of synthetic chemistry. However, the reported methods for the reductive cleavage of isoxazoles have limitations. The most useful method for the reductive cleavage of isoxazoles to *ortho*-amino ketone derivatives is hydrogenation by using precious metals such as Pd [9–13] or Pt [10,11] as catalysts, but substrate groups susceptible to reduction do not survive [12]. Non-precious Raney Ni [14] has also been used in isoxazole hydrogenation, but requires careful handling and fine control of the reaction conditions. Moreover, hydrogenation using H_2 as the reducing agent generally requires harsh conditions such as high temperature and high pressure. In recent years, many researchers have proposed alternative strategies to hydro-

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genation for the reductive cleavage of isoxazoles, via electron transfer by AlI_3 [15], $FeCl_2$ [16–18], $TiCl_3$ [19], SmI_2 [20,21], or Me_3SiI [22,23], but these methods require extremely anhydrous conditions. In addition, non-catalytic stoichiometric reduction processes with $FeSO_4$ [24], $Na_2S_2O_4$ [25,26], $Mo(CO)_6$ [9,11], or CuI [27] as reducing agent have been used in the synthesis of *ortho*-amino ketones. Unfortunately, large amounts of chemical reagents are required and many waste products are formed. The development of clean and highly efficient methods for reductive cleavage reactions under mild reaction conditions is therefore important. This approach is pursuing to resolve the problems that are still encountered in the production of *ortho*-amino ketones via ring opening of isoxazole motifs.

Hydrazine hydrate is a highly active and relatively clean reducing agent with N_2 as the sole byproduct, and it has been widely used under mild reaction conditions in the synthesis of dyes, medical products, and pesticides. Guanidine [28], reduced graphene oxide [29], precious metals [30], and non-precious metal oxides [31,32] have been widely used in catalytic reductions using hydrazine hydrate in organic and inorganic synthesis [33,34]. Hydrazine hydrate is a popular reducing agent in many synthetic fields, but a low-cost and highly efficient catalyst for this synthetic process still needs to be found.

In our previous research [35], hydrazine hydrate was established to be a relatively clean and efficient reducing agent in the ring-opening reaction of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione to 1-amino-2-acetylanthraquinone. The development of more-efficient catalysts is an increasingly important goal for both economic and environmental reasons. The aim of this work was to develop an efficient catalytic system for the reductive ring cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione to yield 1-amino-2-acetylanthraquinone (Scheme 1). To the best of our knowledge, this work firstly represents a highly-efficient approach of Cu catalyzed ring opening of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione for synthesizing 1-amino-2-acetylanthraquinone using hydrazine hydrate as the reducing agent.

2. Experimental

2.1. Materials and instruments

All reagents were purchased from Aladdin and were used without further purification. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained using a Bruker Avance II 400 MHz instrument at room temperature, with tetramethylsilane as the internal standard; coupling constants (*J*) were measured in hertz. Mass spectra (MS) were recorded using an HP1100LC/MSD spectrometer.

2.2. Catalytic reaction

In a typical experimental procedure, 3-methylanthra[1,2-*c*]isoxazole-6,11-dione (2.63 g, 100 mmol) was placed in a one-necked round-bottomed flask (25 mL), and then deionized water (3.0 mL) and 2.6–5 mol% of catalyst were added. The reaction mixture was stirred at room temperature for 30 min to ensure good dispersion, and then the desired amount of hydrazine hydrate was added to the mixture with continuous stirring. The mixture was continuously stirred for the desired reaction time. After the reaction, the mixture was filtered, and the obtained solid product was washed with deionized water and dried at 105 °C overnight. The obtained product was quantitatively analyzed using high-performance liquid chromatography (HPLC). The conversion was calculated as the percentage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione consumed based on the HPLC results. In all cases, more than 95% selectivity for 1-amino-2-acetylanthraquinone (MS, M + 1 = 266) was obtained, and the main byproduct was hydroxy-substituted 1-amino-2-acetylanthraquinone (MS, M + 1 = 283). Red powder, m.p. 222–226 °C; ^{1}H NMR ($CDCl_3$): δ 2.68 (3H, s, CH_3), 7.55 (1H, d), 7.72–7.83 (2H, t), 8.16 (1H, d), 8.23–8.32 (2H, d), 9.51, and 9.92 (2H, s, NH_2); MS (APCI, *m/z*) for 1-amino-2-acetylanthraquinone $[M + 1]^+$ 266.

3. Results and discussion

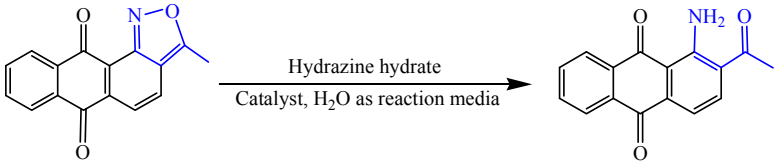
3.1. Effect of transition metal type

Various transition-metal nitrates were screened in the reductive cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione for the synthesis of 1-amino-2-acetylanthraquinone. The results are summarized in Table 1. As shown in Table 1 that the type of transition metal significantly influences the ring-opening reaction. The best catalytic performance was achieved us-

Table 1
Catalytic reduction of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione.

Entry	Catalyst	Conversion [a] (%)
1	$Co(NO_3)_2$	11.6
2	$Ni(NO_3)_2$	10.8
3	$Fe(NO_3)_3$	9.0
4	$Cu(NO_3)_2$	96.8
5	blank	6.5
6 [b]	blank	6.6

Reaction conditions: 5 mol% of catalyst dosage (molar percentage of catalyst to 3-methyl-anthra-[1,2-c]-isoxazol-6,11-dione), 4 equiv. hydrazine hydrate, 3 mL H_2O, room temperature, 1 h.
[a] Determined by HPLC after the reaction (in all cases, the selectivity is above 95%).
[b] Reaction time: 24 h.



Scheme 1. Catalytic reductive ring cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione for highly efficient synthesis of 1-amino-2-acetylanthraquinone using hydrazine hydrate as reducing agent.

Table 2
Catalytic reaction results over different copper salts.

Entry	Catalyst	Time (h)	Conversion[a] (%)
1	$CuSO_4$	1	85.3
2	$CuSO_4$	2	98.3
3	$CuCl_2$	1	78.4
4	$CuCl_2$	2	98.1
5	CuCl	1	96.0
6	Cu	1	86.6
7	Cu	2	94.2
8	$Cu(NO_3)_2$	1	96.8

Reaction conditions: 5 mol% of catalyst dosage, 4 equiv. hydrazine hydrate, 3 mL H_2O, room temperature.
[a] Determined by HPLC after the reaction (in all cases, the selectivity is above 95%).

ing $Cu(NO_3)_2$ as catalyst, giving 96.8% of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione conversion. However, the conversions were only 11.6%, 10.8%, and 9.0% over $Co(NO_3)_2$, $Ni(NO_3)_2$, and $Fe(NO_3)_3$, respectively. The blank experiment results showed that the conversion was only 6.5% when the same reaction conditions were used except for in the absence of $Cu(NO_3)_2$. Even when the reaction time was extended to 24 h, there was still no noticeable increase in the conversion. We can therefore conclude that $Cu(NO_3)_2$ is a promising catalyst for the reductive cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione for the production of 1-amino-2-acetylanthraquinone. Moreover, no detectable reaction occurs in the absence of hydrazine, suggesting that the reaction takes place via a catalytic reduction route; this is different from the reported method [27].

3.2. *Effect of copper salt type*

We then investigated the catalytic performances of various copper salts (Table 2). Under the same reaction conditions, the catalytic activity order was $Cu(NO_3)_2$ > CuCl > Cu > $CuSO_4$ > $CuCl_2$. $Cu(NO_3)_2$ is the best catalyst for this ring-cleavage reaction. In the cases of Cu, $CuSO_4$, and $CuCl_2$, extending the reaction time up to 2 h significantly increased the conversion to 94.2%, 98.3%, and 98.1%, respectively. These results suggest that various copper salts, especially $Cu(NO_3)_2$, are highly-efficient catalysts for the mild and efficient ring cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione to 1-amino-2-acetylanthraquinone with hydrazine hydrate as a relatively clean and highly active reducing agent.

3.3. *Effect of reaction conditions*

The effects of catalyst dosage, reducing agent, and reaction time on the synthesis of 1-amino-2-acetylanthraquinone were further investigated using $Cu(NO_3)_2$ as the catalyst (Table 3). The results showed that 96.2% of conversion (116 g product g^{-1} copper h^{-1}) can be obtained over $Cu(NO_3)_2$ in the presence of 4 equiv. of hydrazine hydrate for 1 h. Even if the amount of hydrazine hydrate is decreased to 1.3 equiv., 97.2% conversion is still obtained in the presence of 2.6 mol% of $Cu(NO_3)_2$ for 2 h. These results indicate that this catalyst system containing

Table 3
Optimum conditions with $Cu(NO_3)_2$ as catalyst.

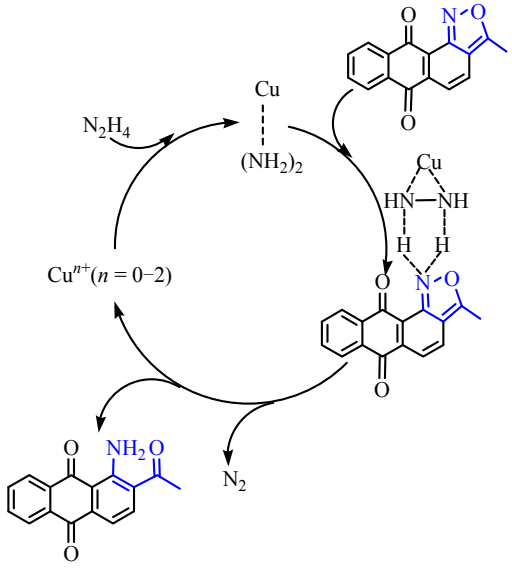
Entry	Catalyst dosage (mol%)	Hydrazine (equiv.)	Time (h)	Conversion[a] (%)
1	5	4	1	96.8
2	2.6	4	1	96.2
3	2.6	2.6	1	85.6
4	2.6	1.3	1	72.6
5	2.6	1.3	2	97.2

Reaction conditions: 3 mL H_2O, room temperature.
[a] Determined by HPLC after the reaction (in all cases, the selectivity is above 95%).

$Cu(NO_3)_2$ and hydrazine hydrate is facile and efficient for the cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione to 1-amino-2-acetylanthraquinone.

3.4. *Plausible reaction mechanism*

Based on the results above, we explored the mechanism of Cu catalysis in the presence of hydrazine hydrate. Table 1 shows that $Cu(NO_3)_2$ is a highly efficient catalyst for the reductive cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione. From Table 2, it can be seen that an in situ reduced low-valent Cu species might be the active species in the $Cu(NO_3)_2$-catalyzed reductive ring opening of the isoxazole motif. We also performed experiments by mixing hydrazine hydrate with diverse transition-metal (Fe, Cu, Co, and Ni) nitrates. It was found that the mixtures became muddy and changed color, suggesting that the high-valent metal ions have been reduced to low-valent ones, and even zero-valent metals. A combination of these phenomena with the results in Tables 1 and 2 suggests that in situ reduced low-valent Cu species may be mainly responsible for the catalytic reduction. We also performed experiments using stoichiometric amounts of Cu metal or CuCl, but without adding hydrazine hydrate; quite low conversions were ob-



Scheme 2. Tentative mechanism for reductive cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione in the presence of Cu catalyst to produce 1-amino-2-acetylanthraquinone.

Graphical Abstract

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Highly efficient and clean synthesis of 1-amino-2-acetylanthraquinone by copper-catalyzed reductive cleavage of isoxazole motif

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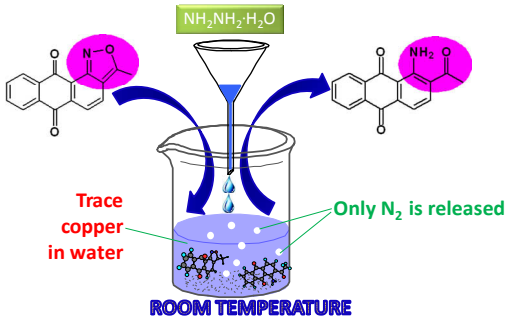
A trace-copper-catalyzed reductive isoxazole-ring-cleavage strategy for clean and highly efficient production of 1-amino-2-acetylanthraquinone under mild reaction conditions was presented.



served. We therefore conjecture that the activation of hydrazine by the formation of a coordinate bond, or activation of the N–H bond of hydrazine, not copper or low-valent copper ions themselves, enhances cleavage of the isoxazole ring [28,32,36]; a plausible reaction mechanism is shown in Scheme 2.

4. Conclusions

In summary, $Cu(NO_3)_2$ was found to be an excellent catalyst for the reductive ring cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione to produce 1-amino-2-acetylanthraquinone using hydrazine hydrate as the reducing reagent in water. 97.2% of conversion and more than 95% of selectivity for 1-amino-2-acetylanthraquinone were obtained using 2.6% of $Cu(NO_3)_2$ to 3-methylanthra[1,2-*c*]isoxazole-6,11-dione and 1.3 equiv. of hydrazine hydrate for 2 h in water. A plausible reaction mechanism was proposed. It was clear that hydrazine hydrate was activated by interactions with Cu species, and this accelerated the ring-opening reaction of 3-methylanthra[1,2-*c*] isoxazole-6,11-dione. We believe that the copper-catalyzed ring cleavage of the isoxazole motif could be used to produce various *ortho*-amino ketones from different isoxazole-containing compounds, opening up a new avenue for mild and efficient reduction procedures in fine chemicals.

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