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Article

Simple primary amine catalyzed aerobic reductive ring-cleavage of isoxazole motif

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ARTICLE INFO

Article history:

Received 25 June 2014

Accepted 18 July 2014

Published 20 February 2015

Keywords:

Organocatalysis

Simple primary amine

Aerobic reductive ring cleavage

1-Amino-2-acetyl anthraquinone

Green chemistry

ABSTRACT

A clean and highly efficient catalytic aerobic reductive ring-cleavage of 3-methylantra[1,2-c]isoxazole-6,11-dione to 1-amino-2-acetylanthraquinone was performed using simple organic amines as organocatalysts and water as a green reaction medium. This method provides a new clean transformation of isoxazole-containing compounds to the corresponding *ortho*-amino ketones. The catalytic performance of various organic amines was carefully screened, and simple organic primary amines were found to be promising practical catalysts with outstanding catalytic performance. Isopropylamine as the organocatalyst gave 97.2% conversion of 3-methylantra[1,2-c]isoxazole-6,11-dione, with 97.2% selectivity to 1-amino-2-acetylanthraquinone, in the presence of oxygen only, using 1 equiv. of hydrazine hydrate at room temperature for 3 h. A possible mechanism is also proposed.

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1. Introduction

ortho-Amino ketones, a series of important organic intermediates, are widely used in the dye, pigment, medical, and petrochemical fields [1–3]. Recently, the preparation of *ortho*-amino ketones has attracted much attention. The synthesis of this type of amino ketone via ring cleavage of an isoxazole motif is an efficient strategy, e.g., for the synthesis of 1-amino-2-acetylanthraquinone for Vat blue 66 [4].

Stoichiometric reduction processes have generally been used in the synthesis of *ortho*-amino ketones, with ferrous sulfate [5], sodium hydrosulfite [6], Mo(CO)₆ [7], CuI [8], EtMgBr/Ti(Oi-Pr) [9], or sodium [10] as reducing agents. However, large amounts of chemical reagents are required, and large amounts of wastes are produced. The heavy pollution caused by this process is inconsistent with the increasing de-

mands of green chemistry. The search for a clean and efficient method for reductive cleavage under mild reaction conditions is therefore important. Electron-transfer reactions by AlI₃ [11], iron dichloride [12–14], TiCl₃ [15], SmI₂ [16,17] or iodotrimethylsilane [18,19] are feasible alternative strategies for isoxazole cleavage, but stringent anhydrous conditions are essential, and heavy pollution cannot be avoided. The development of clean methods for synthesizing *ortho*-amino ketones such as 1-amino-2-acetylanthraquinone, an important dye intermediate, is therefore desirable.

To overcome the above issues, catalytic hydrogenation, which is a clean method, has been used in the ring-cleavage of isoxazole motifs for the production of *ortho*-amino ketone derivatives. Precious metals such as palladium or platinum [20–23] and non-precious metals such as Raney nickel efficiently catalyze the production of various isoxazole motifs [24].

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This work was supported by the Chinese Ministry of Education via the Program for New Century Excellent Talents in University (NCET-12-0079) and the Fundamental Research Funds for the Central Universities (DUT12LK51).

DOI: 10.1016/S1872-2067(14)60200-X | <http://www.sciencedirect.com/science/journal/18722067> | Chin. J. Catal., Vol. 36, No. 2, February 2015

The high costs and poor availability of precious metals limit their extensive use, and careful handling and finely controlled reaction conditions are required if Raney nickel is used. We previously demonstrated that copper can efficiently catalyze this reaction for the clean synthesis of *ortho*-amino ketones, including 1-amino-2-acetylanthraquinone [25]. However, the problem of pollution by residual transition metals still needs to be resolved. The search for metal-free highly efficient catalysts for catalytic hydrogenation reactions for *ortho*-amino ketone production is therefore important.

Organocatalysis, or the use of small organic molecules to catalyze organic transformations, is a relatively new and popular research field. Although chemical transformations that use organocatalysts have been documented sporadically over the past century, it was not until the late 1990s that the field of organocatalysis was born, based on a small number of articles that inspired an explosion of research. Between 1998 and 2008, the field of organocatalysis grew rapidly, and at least 1500 papers describing the use of organocatalysts in more than 130 discrete reaction types were published [25,26]. Organocatalytic methods have also been used in hydrogenations [27–29] and ring-opening reactions [30]. In our previous research [31], dimethyl formamide (DMF)-promoted ring-opening reactions of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione to 1-amino-2-acetylanthraquinone were established. However, a large amount of DMF, which is poisonous, and excess hydrazine are required to obtain a good catalytic performance. The development of more efficient organocatalysts, with water as a clean solvent, is an increasingly important goal for chemists, for both economic and environmental reasons. Simple and complex organic amines are popular organocatalysts, and have been extensively used in many transformations, with excellent results [32–34]. However, the catalytic performance of organic amines in ring cleavage of isoxazole-containing compounds to produce the corresponding *ortho*-amino ketones has not been investigated.

In this study, using the ring cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione to produce 1-amino-2-acetylanthraquinone as a model reaction (Scheme 1), we explored the possibility of using simple amines as organocatalysts for the ring cleavage of isoxazole motifs to produce the corresponding *ortho*-amino ketones. The aim of the present work is to construct a clean and efficient strategy for the synthesis of 1-amino-2-acetylanthraquinone via a ring-opening route, by the reduction of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione in the presence of organocatalysts. An excellent catalytic performance was achieved using isopropylamine as the catalyst, and 97.2% 3-methylanthra[1,2-*c*]isoxazole-6,11-dione conversion, with 97.2% 1-amino-2-acetylanthraquinone selectivity, was achieved. It has been shown [27] that oxygen is important in guanidine-catalyzed selective hydrogenation of olefins using

aqueous hydrazine as the reducing reagent; we therefore thought that oxygen in the air could be used in the amine-catalyzed reductive ring-cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione. A possible mechanism for the highly efficient amine-catalyzed transformation in the presence of air is also proposed. The organic-amine-catalyzed aerobic reductive ring-cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione can be extended to other isoxazole-containing compounds to produce the corresponding *ortho*-amino ketones.

2. Experimental

2.1. Materials and instruments

All reagents were purchased from Aladdin and were used without further purification. ^1H nuclear magnetic resonance (NMR) spectroscopy was performed using a Bruker Avance 400M instrument at room temperature, with tetramethylsilane as the internal standard; coupling constants (*J*) were measured in hertz; mass spectrometry (MS) was performed using an HP1100LC/MSD instrument.

2.2. Catalytic performance measurement

In a typical experimental procedure, 3-methylanthra[1,2-*c*]isoxazole-6,11-dione was placed in a 25 mL one-necked round-bottomed flask, and deionized water (3.0 mL, a green reaction medium) and an appropriate amount of isopropylamine were introduced. The reaction mixture was stirred at room temperature for 30 min to obtain good dispersion, and the desired amount of hydrazine hydrate was then added, with continuous stirring. The mixture was continuously stirred for the desired reaction time. The product was insoluble in water, and was easily separated by filtration. After the reaction, the mixture was filtered, and the solid product was washed with deionized water and dried at 105 °C overnight. The product was quantitatively analyzed using high-performance liquid chromatography (HPLC). The conversion was calculated, based on the HPLC results, as the ratio of the consumed amount to the total amount of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione, expressed as a percentage. The product was characterized using ^1H NMR and MS spectroscopies. Characterization results: red powder, mp 222–226 °C; ^1H 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 type of organic amine

The molecular structure of the product obtained via organic-amine-catalyzed ring-cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione was determined using ^1H NMR and MS spectroscopies. The results confirm that the molecular structure is 1-amino-2-acetylanthraquinone, i.e., the desired product was successfully obtained using organic-amine-catalyzed

Scheme 1. Synthesis of 1-amino-2-acetylanthraquinone.

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

Entry	Catalyst	Conversion (%)	Selectivity (%)
1	<i>iso</i> -C ₃ H ₇ NH ₂	95.4	98.5
2	CH ₃ CH ₂ NH ₂	95.3	98.1
3	CH ₃ NH ₂	91.8	97.7
4	(CH ₃) ₂ NH	81.9	97.6
5	(<i>iso</i> -C ₃ H ₇) ₂ NH	48.5	95.7
6	(CH ₃) ₃ N	43.7	94.7
7	Pyridine	21.2	86.5
8	NH ₃ ·H ₂ O	26.1	91.2
9*	—	9.6	67.9

Reaction conditions: hydrazine hydrate 8 equiv., room temperature (25 °C), reaction time 1 h (* 3 h), total water volume 3.0 mL, catalyst dosage 10 mmol (organic amine).

ring-cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione. Various organic amines were tested as organocatalysts in the reaction. The results are summarized in Table 1.

The data in Table 1 show that the best catalyst was isopropylamine, giving 95.4% 3-methylanthra[1,2-*c*]isoxazole-6,11-dione conversion and 98.5% selectivity for 1-amino-2-acetylanthraquinone (Table 1, entry 1). To confirm that the added organic amine catalyzed the reaction, a blank experiment was performed; only 9.6% conversion (Table 1, entry 9) was achieved under the same conditions in the absence of an organic amine, clearly confirming the catalytic effect. The catalytic performance of various simple organic amines in the ring cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione was explored; pyridine and aqueous ammonia were included for comparison. The data in Table 1 show that primary amines exhibited excellent catalytic efficiency, and the conversions reached 95.4%, 95.3%, and 91.8% using isopropylamine, CH₃CH₂NH₂, CH₃NH₂, respectively, as catalysts (Table 1, entries 1–3). However, except for (CH₃)₂NH (Table 1, entry 4), secondary and tertiary amines had poor catalytic activity; this may be because steric hindrance inhibits attack of the isoxazole by the amine-hydrazine complex. This conclusion is supported by a comparison of the catalytic activity of CH₃NH₂, (CH₃)₂NH, and (CH₃)₃N (91.8%, 81.9%, and 43.7%, respectively). We consider that the electron-donating group influences the electron cloud density of the lone pair of electrons on the nitrogen atom, resulting in different activation degrees of hydrazine hydrate. Pyridine was also used as the catalyst, but its catalytic activity was significantly lower than those of other organic amines, possibly because the electron cloud density of the nitrogen lone pair electrons is lower. NH₃·H₂O also had low activity, which shows that the catalytic effect of organic amines arises from the lone pair of electrons on the nitrogen atom, rather than the alkalinity.

Although the catalytic efficiency of CH₃CH₂NH₂ is close to that of isopropylamine, its toxicity is twice that of isopropylamine (820 and 400 mg/kg of LD₅₀ for isopropylamine and CH₃CH₂NH₂, respectively). These results show that isopropylamine is clean and highly efficient, and is the best organocatalyst for the reductive ring-cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione to 1-amino-2-acetylanthraquinone.

3.2. Optimization of reaction conditions

Table 2

Optimization of reaction conditions.

Entry	Hydrazine hydrate (equiv.)	<i>iso</i> -C ₃ H ₇ NH ₂ (mol)	Time (h)	Conversion (%)	Selectivity (%)
1	8	0.01	1	95.4	98.5
2	4	0.01	1	65.2	96.6
3	4	0.01	3	94.0	98.1
4	2	0.01	3	63.0	97.3
5	2	0.02	3	97.7	98.3
6	1	0.02	3	97.2	97.2

Reaction conditions: room temperature (25 °C), total water volume 3.0 mL.

The reaction conditions for the isopropylamine-catalyzed ring-cleavage reaction were optimized; the results are summarized in Table 2. The data in Table 2 show that the results of the catalytic ring-cleavage reaction are strongly dependent on the reaction conditions; 97.2% conversion and 97.2% selectivity for 1-amino-2-acetylanthraquinone were obtained using *iso*-propylamine (0.02 mol) and hydrazine hydrate (1 equiv.) at room temperature for 3 h, with water as the clean reaction medium.

3.3. Plausible catalytic reaction mechanism with organic amines

We explored the mechanism of the simple organic-amine-catalyzed ring-cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione via reduction using hydrazine hydrate as the reducing reagent. The data in Table 1 show that primary amines are highly efficient catalysts for isoxazole cleavage. In aqueous solution, the order of the alkalinity of amines is secondary amine > primary amine > tertiary amine, but in isoxazole cleavage, the catalytic efficiency order is primary amine > secondary amine > tertiary amine > ammonia solution (Table 1). The reducing ability of hydrazine hydrate is generally high under alkaline conditions, but in our work, the activity was not directly related to the alkalinity; this further confirms that the catalytic effect of the organic amine comes from hydrazine hydrate activation by the lone pair of electrons on the nitrogen atom rather than enhancement of its reducing power by the alkalinity of the reaction medium. The steric hindrance of branched amines may prevent the amine-hydrazine complex attacking the substrate, and, as a result, the primary amine exhibits high catalytic activity. We therefore conjecture that the catalytic effect of simple organic amines arises from the formation of an amine-hydrazine complex by hydrogen-bond formation, followed by attack on the substrate by the complex. A plausible reaction mechanism for the developed approach is shown in Scheme 2.

Scheme 2. Plausible mechanism for reductive cleavage of 3-methylanthra[1,2-*c*]isoxazole-6,11-dione to 1-amino-2-acetylanthraquinone in the presence of organic amine catalysts.

4. Conclusions

Simple primary amines are highly efficient organocatalysts for ring-opening reactions of isoxazoles via catalytic aerobic reduction with hydrazine hydrate as the reducing reagent and water as the green reaction medium. The primary-amine-catalyzed ring-cleavage of 3-methylanthra[1,2-c]isoxazole-6,11-dione can be used for the clean and efficient synthesis of 1-amino-2-acetylanthraquinone, a useful dye intermediate. Primary amines are promising catalysts, with excellent catalytic performance; 97.2% conversion and 97.2% selectivity were obtained in the presence of isopropylamine (0.02 mol) using of (hydrazine hydrate 1 equiv.) at room temperature for 3 h. This method could be extended to other isoxazole-containing compounds to produce the corresponding *ortho*-amino ketones, including, but not limited to, 1-amino-2-acetylanthraquinone.

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Graphical Abstract

Chin. J. Catal., 2015, 36: 204–208 doi: 10.1016/S1872-2067(14)60200-X

Simple primary amine catalyzed aerobic reductive ring-cleavage of isoxazole motif

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A simple organic-primary-amine-catalyzed aerobic reductive isoxazole ring-cleavage strategy for clean and highly efficient 1-amino-2-acetylanthraquinone production was described.

小分子伯胺催化异噁唑有氧还原开环反应

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摘要: 有机催化是催化领域的前沿. 在水介质中, 以水合肼作为还原剂研究了小分子有机胺催化3-甲基蒽醌-[1,2-c]-异噁唑有氧还原开环反应高效合成1-氨基-2-乙酰基蒽醌, 详细考察了不同种类有机胺对异噁唑有氧还原开环反应的催化性能, 发现小分子有机伯胺具有很好的还原开环催化性能. 在1倍水合肼存在下室温反应3 h, 3-甲基蒽醌-[1,2-c]-异噁唑转化率和目标产物1-氨基-2-乙酰基蒽醌选择性均可达到97.2%. 产物的分子结构经氢核磁谱和质谱得以确证. 此外, 提出了小分子有机伯胺催化3-甲基蒽醌-[1,2-c]-异噁唑有氧还原开环反应合成1-氨基-2-乙酰基蒽醌的可能反应机理.

关键词: 有机催化; 小分子伯胺; 有氧还原开环; 1-氨基-2-乙酰基蒽醌; 绿色化学

收稿日期: 2014-06-25. 接受日期: 2014-07-18. 出版日期: 2015-02-20.

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基金来源: 教育部新世纪优秀人才支持计划(NCET-12-0079); 中央高校基本科研业务费专项资金(DUT12LK51).

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