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Original article

Synthesis of novel 1,3-oxazole derivatives with insect growth-inhibiting activities

Peng Guo, Jun-Hai Huang, Qing-Chun Huang, Xu-Hong Qian *

Shanghai Key Laboratory of Chemical Biology, Institute of Pesticides and Pharmaceuticals, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

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ABSTRACT

Straightforward and direct synthesis of 2-substituted-5-oxazolecarbaldehydes was achieved by treating propargylamides with mercury(II) perchlorate as catalyst and ammonium cerium(IV) nitrate as oxidant agent through intramolecular cyclization. These structurally interesting outcomes benefit to synthesize 2,5-disubstituted-1,3-oxazoles with armyworm growth regulating activities.

1. Introduction

Oxazole nucleus has gained much attention recently because of its application in organic synthesis and its biological and pharmaceutical properties in numerous natural and unnatural structures [1–6]. Several strategies (Scheme 1) have been developed for transition metals (Au or Pd) catalyzed intramolecular efficient and direct preparation of functionalized oxazoles under mild condition [7–13]. Broggini described the synthesis of oxazolecarbaldehydes by Pd(II) complex catalyzed alkyne oxidation using a stoichiometric amount of reoxidant agent [7]. Hashmi reported the efficient protocol to functionalized oxazoles from the combination gold(I) complex catalysis and dioxygen oxidation [13]. We recently found equivalent amounts of mercury(II) perchlorate hydrate could also rapidly prompt propargylamides to generate oxazolecarbaldehydes by intramolecular cyclization and oxidation reaction [14]. This condition has potential for establishing a new valuable alternative to the formylation on oxazole rings because the reactant is more low-cost and easily accessible than Au or Pd complexes. In order to reduce toxicity and pollution caused by mercury(II), following optimization study was performed and offered a more accessible method to directly transform propargylamides to oxazolecarbaldehydes with mercury(II) perchlorate as catalyst and ammonium cerium(IV) nitrate as oxidant agent.

In addition, these structurally interesting outcomes benefit to synthesize 2,5-disubstituted-1,3-oxazoles by straightforward synthetic route. Many insecticidal active structures comprise nitrogen- and oxygen-containing five-membered heterocycle as key pharmacophore (Fig. 1) [15–18]. 1,3-Oxazole cores have also been reported with insecticidal activities [19,20], but they have never been used as insect growth regulators. These structure and activity relationships inspired us to synthesize a series of novel asymmetrical 2,5-disubstituted-1,3-oxazole derivatives and measure their bioactivities.

2. Experimental

All reagents were of analytic grade and obtained from commercial suppliers and used without further purification. Melting points were measured in an open capillary using Büchi melting point B-540 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz and 100 MHz, respectively) using TMS as the internal standard. High resolution mass spectra (HRMS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument.

The synthetic route of our target oxazole derivatives is outlined in Scheme 2. The starting material can be easily obtained by the described condition. The effective and straightforward synthesis of 2-phenyl-5-oxazolecarbaldehydes was performed by intramolecular reaction of propargylamides through treatment with a catalytic amount of mercury(II) perchlorate hydrate in the presence of ammonium cerium(IV) nitrate as oxidant agent. Then

* Corresponding author.
E-mail address: xhqian@ecust.edu.cn (X.-H. Qian).

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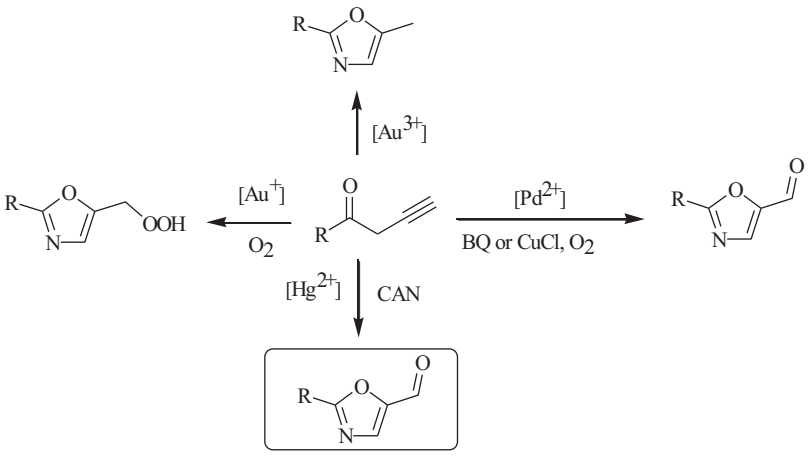

Scheme 1. Transition metals catalyzed intramolecular efficient and direct preparations of functionalized oxazoles.

1,3-oxazole derivatives could be easily received quantitively by performing a Schiff condensation in methanol in the presence of corresponding 5-oxazolecarbaldehydes and anilines following reducing reaction with sodium borohydride.

General procedure for the synthesis of ***b1–6:*** Mercury(II) perchlorate trihydrate (0.05 equiv.) and ceric ammonium nitrate (0.4 equiv.) was added to a solution of **a** (1 equiv.) in acetonitrile. The mixture was stirred at room temperature for about 1 h until the completion of conversion of **a** to **b** (monitored by TLC), and then poured to dichloromethane. The undissolved substance was removed by filtration. The filtrate was concentrated *in vacuo* to give a residue, which was purified by silica gel column chromatography to give **b**. Yield 30%–40%.

General procedure for the synthesis of ***c1–20:*** The mixture of **b** (1 equiv.) and corresponding aniline (1 equiv.) in methanol was stirred at room temperature for about 10 h until the completion of reaction (monitored by TLC). Then sodiumborohydride (2 equiv.) was added to the solution, and then stirred at room temperature for another 10 min. The mixture was treated with water and extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo* to give a residue, which was purified by recrystallization with petroleum ether to give **c**. Yield 70%–90%.

All of the final products were characterized by mp, ^{1}H NMR, ^{13}C NMR and high-resolution mass spectra (HR-MS) data. The growth regulating activities of compounds against third-instar Oriental armyworm were evaluated by foliar application using the reported procedure [21]. For the foliar armyworm tests, individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 third-instar Oriental armyworm larvae. Weight inhibition rate of survival armyworm was evaluated 2 days after treatment. The biological data in Table 1 was the average value of the three tested values.

3. Results and discussion

Our previous research found that equivalent amounts of mercury(II) perchlorate hydrate could prompt propargylamide to transfer to oxazolecarbaldehyde in 5 min at room temperature (Scheme 3). To reduce the amount of mercury because of its toxicity, we first investigated the effect of the amount to this intramolecular cyclization reaction. It turned out that the catalytic amount of mercury was an efficient catalyst to generate alkylideneoxazoline with high reaction rate. We speculated that redundant mercury(II) might supply oxidizability to facilitate the produce of aldehyde group. Then ammonium cerium(IV) nitrate was selected to replace redundant mercury(II) as oxidant agent because it has been reported as an oxidant to transform aromatic side chains to aldehyde group [22]. The results showed this condition could achieve the same effect as equivalent amounts of mercury(II) and reduce cost and environmental pollution.

3.1. Characteristic data of compounds

2-(2,4-Dichlorophenyl)oxazole-5-carbaldehyde (**b1**): Yellowish solid; mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.11 (d, 1H, J = 8.8 Hz), 8.02 (s, 1H), 7.60 (s, 1H), 7.42 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 162.4, 149.7, 138.5, 137.8, 134.3, 132.4, 131.5, 127.6, 123.3.

2-Phenyloxazole-5-carbaldehyde (**b2**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 8.20 (dd, 2H, J = 8.4 Hz, 1.6 Hz), 7.98 (s, 1H), 7.64–7.48 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 165.4, 149.5, 139.0, 132.2, 129.0, 127.6, 125.8. MS: 173, 144, 116.

2-(4-Chlorophenyl)oxazole-5-carbaldehyde (**b3**): White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.10 (d, 2H, J = 6.8 Hz), 7.93 (s, 1H), 7.48 (d, 2H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 164.5, 149.7, 139.1, 138.7, 129.5, 129.0, 124.4.

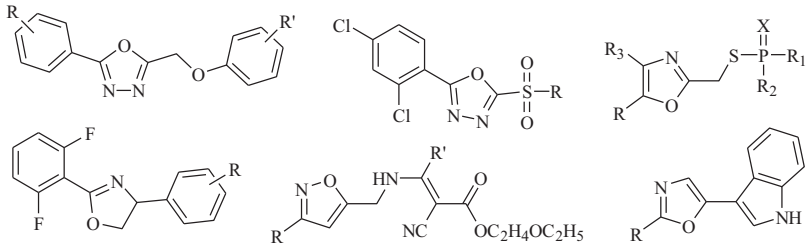

Fig. 1. Insecticidal compounds with nitrogen- and oxygen-containing five-membered heterocycle.