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Article

Selenium-catalyzed oxidative carbonylation of 2-aminobenzyl alcohol to give 1,4-dihydro-2H-3,1-benzoxazin-2-one

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ABSTRACT

An efficient, economical, and phosgene-free approach was developed for the preparation of 1,4-dihydro-2H-3,1-benzoxazin-2-one from 2-aminobenzyl alcohol. In terms of its key features, this reaction uses the cheap and recyclable non-metal selenium as a catalyst instead of the noble metal palladium; carbon monoxide as a carbonylation agent instead of virulent phosgene or one of its derivatives; and oxygen as an oxidant. The selenium-catalyzed oxidative carbonylation reaction of 2-aminobenzyl alcohol proceeded efficiently in a single pot in the presence of triethylamine to afford 1,4-dihydro-2H-3,1-benzoxazin-2-one in 87% yield. Furthermore, the selenium catalyst was readily recovered and recycled, affording a product yield of 80% after five cycles.

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1. Introduction

1,4-Dihydro-2H-3,1-benzoxazin-2-one is an important structural motif that can be found in a wide range of biologically active compounds. For example, efavirenz, which is a non-nucleoside reverse transcriptase inhibitor for the treatment of HIV infections, consists of a substituted 1,4-dihydro-2H-3,1-benzoxazin-2-one core [1–3]. Several other compounds containing this structural motif have been reported to be orally active nonsteroidal progesterone receptor antagonists, which could be used for the treatment of hormone-dependent cancers [4–6]. 1,4-Dihydro-2H-3,1-benzoxazin-2-one also represents a useful tool compound in organic synthesis for the preparation of aza-*ortho*-xylylene via a thermal decarboxylation reaction [7–9]. In light of the many uses of this compound, considerable

research efforts have been directed towards the development of efficient methods for its synthesis. Traditionally, 1,4-dihydro-2H-3,1-benzoxazin-2-one has been readily prepared by the reaction of 2-aminobenzyl alcohol with phosgene [10] or a suitable alternative such as chloroformate [11], triphosgene [12], urea [13] or *N,N'*-carbonyldiimidazole (CDI) [5]. However, there are several drawbacks associated with these methods, including high toxicity, low atom economy and the emission of the corrosive waste products. Selenium- [14,15] and palladium-catalyzed [16] reactions have been developed for the preparation of 1,4-dihydro-2H-3,1-benzoxazin-2-one by the carbonylation of 2-nitrobenzyl alcohol with carbon monoxide. Unfortunately, only one third of the CO consumed during these reactions is transferred to the product, with the other two thirds being converted to the greenhouse gas CO₂ as a byprod-

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2.2. Typical procedure for the oxidative carbonylation of 2-aminobenzyl alcohol to give 1,4-dihydro-2H-3,1-benzoxazin-2-one

Colorless needles; mp 123–124 °C (lit. [14] 118–119 °C); ^1H NMR (400 MHz, CDCl_3) δ = 8.36 (s, 1H), 7.28 (d, J = 12.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 5.34 (s, 2H).

2.1. General

3.1. Preparation of 1,4-dihydro-2H-3,1-benzoxazin-2-one

It was envisaged that the selenium-catalyzed oxidative carbonylation of 2-aminobenzyl alcohol could be conducted in a one-pot manner with carbon monoxide and oxygen. In practice, this reaction proceeded smoothly to give the desired product 1,4-dihydro-2*H*-3,1-benzoxazin-2-one and water, together with a small amount of 1,3-bis(2-(hydroxymethyl)phenyl)urea, suggesting the competitive intermolecular *N*-carbonylation of 2-aminobenzyl alcohol. 2-Aminobenzyl alcohol reached complete conversion after 5 h when the reaction was conducted at 150 °C, affording 1,4-dihydro-2*H*-3,1-benzoxazin-2-one in 87% yield (Table 1, entry 2). The outcome of the reaction appeared to be sensitive to the temperature. For example, the reaction failed to reach the complete conversion of 2-aminobenzyl al-

Scheme 1. Previous and present synthetic approaches to 1,4-dihydro-2*H*-3,1-benzoxazin-2-one.

Table 1Preparation of 1,4-dihydro-2*H*-3,1-benzoxazin-2-one under various conditions.

Entry	<i>t</i> (h)	<i>T</i> (°C)	Se (mmol)	Base	Et ₃ N (mmol)	<i>P</i> (CO)/ <i>P</i> (O ₂) (MPa)	Solvent	<i>X</i> ^a /%	<i>Y</i> ^b /%
1	4	150	0.2	Et ₃ N	5	2/0.5	THF	79	56
2	5	150	0.2	Et ₃ N	5	2/0.5	THF	100	87
3	5	140	0.2	Et ₃ N	5	2/0.5	THF	83	66
4	5	160	0.2	Et ₃ N	5	2/0.5	THF	100	85
5	5	150	0	Et ₃ N	5	2/0.5	THF	0	0
6	5	150	0.1	Et ₃ N	5	2/0.5	THF	53	38
7	5	150	0.3	Et ₃ N	5	2/0.5	THF	100	86
8	5	150	0.2	—	5	2/0.5	THF	34	21
9	5	150	0.2	NaOH	5	2/0.5	THF	34	21
10	5	150	0.2	K ₂ CO ₃	5	2/0.5	THF	34	21
11	5	150	0.2	NaOAc	5	2/0.5	THF	43	30
12	5	150	0.2	C ₅ H ₅ N	5	2/0.5	THF	45	27
13	5	150	0.2	Et ₃ N	1	2/0.5	THF	45	39
14	5	150	0.2	Et ₃ N	10	2/0.5	THF	100	86
15	5	150	0.2	Et ₃ N	5	1/0.5	THF	68	32
16	5	150	0.2	Et ₃ N	5	2/1.0	THF	100	86
17	5	150	0.2	Et ₃ N	5	3/0.5	THF	100	86
18	5	150	0.2	Et ₃ N	5	2/0.5	—	32	20
19	5	150	0.2	Et ₃ N	5	2/0.5	Acetone	32	20
20	5	150	0.2	Et ₃ N	5	2/0.5	EtOAc	70	54
21	5	150	0.2	Et ₃ N	5	2/0.5	DMF	75	57
22	5	150	0.2	Et ₃ N	5	2/0.5	CH ₂ Cl ₂	82	64
23	5	150	0.2	Et ₃ N	5	2/0.5	Toluene	85	70

Reaction conditions: 2-aminobenzyl alcohol (2 mmol), base (5 mmol) and solvent (5 mL).

^a Conversion of 2-aminobenzyl alcohol. ^b Isolated yield of 1,4-dihydro-2*H*-3,1-benzoxazin-2-one.

cohol when it was conducted at 140 °C for 5 h (Table 1, entry 3). Increasing the reaction temperature led to an increase in the conversion of 2-aminobenzyl alcohol, which reached 100% at 150 °C (Table 1, entry 2). Further increasing the temperature did not led to any further improvements in the efficiency of the reaction (Table 1, entry 4). Experimental results indicated that the selenium catalyst was critical to the success of the current catalytic system. Notably, the carbonylation reaction did not proceed in the absence of selenium (Table 1, entry 5). However, the reaction proceeded smoothly with as little as 0.1 equivalent of selenium (Table 1, entry 2). Further increasing the selenium loading failed to lead to further increases in the product yield (Table 1, entry 7). Strongly alkaline conditions are generally required for selenium-catalyzed carbonylation reactions to promote the formation of the active carbonyl selenide species (COSe). With this in mind, we proceeded to examine the effects of several bases on the carbonylation reaction. Although 2-aminobenzyl alcohol can act as a base, the reaction proceeded poorly in the absence of an additional base (Table 1, entry 8). Several common bases, including NaOH, K₂CO₃, NaOAc, pyridine (C₅H₅N) and Et₃N were tested in the current reaction, and the results revealed that Et₃N gave the best results (Table 1, entries 2 and 9–12). We subsequently screened several doses of this base and found that 2.5 equivalents gave the optimum results (Table 1, entries 2, 13 and 14). We also investigate the ratio of CO to O₂ used in this reaction and found 2 MPa CO together with 0.5 MPa O₂ gave the best results (Table 1, entries 2 and 15–17). The carbonylation reaction proceed poorly in the absence of a solvent (Table 1, entry 18), which promoted us to seek a proper solvent for this reaction. Several common solvents we screened, including THF, acetone, EtOAc, DMF, CH₂Cl₂

and toluene, and the results revealed that the reaction performed most effectively with THF, followed by toluene (Table 1, entries 2 and 19–23).

3.2. Phase-transfer catalysis function of selenium catalyst

One remarkable advantage of the current catalytic system is that the selenium catalyst has all of the functional characteristics of a phase-transfer catalyst, in that it cannot only efficiently catalyze the desired transformation, but can also be readily recovered from the reaction mixture. We noted that the selenium powder was generally insoluble in the media prior to the reaction, making the catalytic system heterogeneous at this stage in the process. However, during the reaction process, the selenium dissolved completely to form a homogeneous solution, allowing it to efficiently catalyze the carbonylation reaction. Upon completion of the reaction, the selenium powder precipitated from the reaction media via an oxidation reaction in air, allowing for the catalyst to be readily recovered by suction filtration. Notably, the recovered selenium could be recycled without any discernible decrease in its catalytic performance [14,24]. For example, the selenium catalyst gave a product yield of 80% after five cycles.

3.3. Proposed reaction pathway

A plausible mechanism for the formation of 1,4-dihydro-2*H*-3,1-benzoxazin-2-one is shown in Scheme 2. The reaction of selenium with carbon monoxide in the presence of Et₃N would give the active COSe species **A** [25,26]. The nucleophilic attack of 2-aminobenzyl alcohol to **A** would generate intermediate **B**

Scheme 2. Proposed mechanism for the synthesis of 1,4-dihydro-2H-3,1-benzoxazin-2-one.

[25,27], which would undergo an intramolecular nucleophilic addition from the hydroxyl group on **B** to give the desired product 1,4-dihydro-2H-3,1-benzoxazin-2-one. This step would be accompanied by the release of H_2Se (**C**), which would be oxidized with oxygen to give selenium, thereby completing the catalytic cycle [27].

4. Conclusions

We have developed an efficient and economical approach for the synthesis of 1,4-dihydro-2H-3,1-benzoxazin-2-one from 2-aminobenzyl alcohol. The key features of this reaction include the use of the cheap and recyclable non-metal selenium as a catalyst instead of the noble metal palladium; carbon monoxide as a carbonylation agent instead of virulent phosgene or one of its derivatives; and oxygen as an oxidant. Under these conditions, the selenium-catalyzed carbonylation of 2-aminobenzyl alcohol proceeded efficiently in the presence of triethylamine to afford the desired product 1,4-dihydro-2H-3,1-benzoxazin-2-one in 87% yield. Overall, this process represents

a low cost, atom economical, one-pot, phosgene-free process for the preparation of 1,4-dihydro-2H-3,1-benzoxazin-2-one without the formation of any corrosive waste or carbon dioxide, making this approach a particularly promising alternative to the existing procedures.

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Graphical Abstract

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Selenium-catalyzed oxidative carbonylation of 2-aminobenzyl alcohol to give 1,4-dihydro-2H-3,1-benzoxazin-2-one

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1,4-Dihydro-2H-3,1-benzoxazin-2-one was prepared in 87% yield via the one-pot selenium-catalyzed oxidative carbonylation of 2-aminobenzyl alcohol. The selenium catalyst was readily recovered and recycled.

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硒催化 2-氨基苄醇氧化羰基化合成 1,4-二氢-2H-3,1-苯并噁嗪-2-酮

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摘要: 1,4-二氢-2H-3,1-苯并噁嗪-2-酮作为一种重要的母体骨架广泛存在于生物活性化合物中。此外, 在有机合成中它可作为经受热脱羧生成氮杂-邻二亚甲基苯的有效工具。文献报道的合成 1,4-二氢-2H-3,1-苯并噁嗪-2-酮的方法有: 2-氨基苄醇与光气或其替代物反应, 钌或硫催化的 2-氨基苄醇与 CO 的羰基化反应, 钌或硒催化的 2-硝基苄醇与 CO 的羰基化反应, 钌催化的 2-叠氮基苄醇直接羰基化反应或 2-叠氮基苄醇的氮杂-维悌希 (aza-Wittig)/杂累积多烯调节的环合反应, 苯并呋喃酮的胺解-霍夫曼重排反应, 硼氢化锂还原 1,2-二氢-3,1-苯并噁嗪-2,4-二酮, 以及 2-羟甲基苯基氨基甲酸酯的分子内亲核取代反应。上述合成方法存在原料毒性高或成本高且来源不便、原子经济性低、有腐蚀性废物或 CO₂ 排放、CO 利用率低、催化剂昂贵且难以循环使用、反应步骤较多等缺陷, 因此发展绿色、高效、经济的合成新途径具有重要意义。

本文采用廉价易得的非金属硒作催化剂, 用 CO 作羰基化试剂, O₂ 作氧化剂, 通过硒催化 2-氨基苄醇的氧化羰基化反应直接合成了目标产物 1,4-二氢-2H-3,1-苯并噁嗪-2-酮。通过考察反应时间、反应温度、催化剂硒的用量、助催化剂种类及用量、CO 和 O₂ 的比例及溶剂种类等影响因素, 得到了优化的反应条件, 目标产物收率最高可达 87%。

实验证实, 该 Se/CO 催化体系具有相转移催化功能。反应前硒以粉末形式存在于反应体系中, 为多相体系; 反应开始后, 硒粉参与羰基化反应形成可溶性化合物, 从而成为均相体系; 反应完成后硒粉经氧化可重新从反应介质中沉淀析出, 又变为多相体系。因此, 该体系既实现了高效的均相催化反应, 又便于催化剂分离回收, 且回收的硒可重复使用, 其催化活性基本保持不变。结合相关文献, 我们提出了该反应的机理: 在助催化剂三乙胺存在下, 硒首先与 CO 反应原位生成羰基硒, 然后羰基硒先后接受 2-氨基苄醇中氨基和羟基的亲核进攻生成目标产物, 同时释放出硒化氢, 硒化氢再被 O₂ 氧化为硒, 从而进入下一轮催化循环反应。

总之, 我们成功开发出一条绿色、高效、经济的 1,4-二氢-2H-3,1-苯并噁嗪-2-酮合成新途径。用廉价易得且能循环使用的硒替代贵金属钌作催化剂, 用 CO 替代剧毒光气或其衍生物作羰基化试剂, O₂ 作氧化剂, 硒催化的 2-氨基苄醇氧化羰基化反应可顺利进行, 以 87% 的良好收率得到目标产物, 具有成本低、原子经济性高、CO 利用率高、步骤简短、无腐蚀性废物或温室气体 CO₂ 排放、无光气使用及环境相对友好等优点。

关键词: 硒; 氧化羰基化; 1,4-二氢-2H-3,1-苯并噁嗪-2-酮; 2-氨基苄醇; 相转移催化

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