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Fe-Catalyzed Synthesis of 2-Benzoxazolone—An Important Fragment of Biologically Active Compounds †

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Abstract: 2-Benzoxazolone, as well as its derivatives, are valuable structural fragments of a number of important biologically active substances. 2-Benzoxazolone derivatives are promising as antitumor, antimicrobial, antiretroviral, anticonvulsant, tranquilizing, and insecticidal agents. 2-Benzoxazolone is usually produced by the condensation of o-aminophenol with urea, phosgene, and other carbonic acid derivatives. There are also methods for the synthesis of 2-benzoxazolone from salicylamide with trichloroisocyanuric acid as a chlorinating agent, from hydroxybenzoic acid using ammonium azide and the Vilsmeier complex. The disadvantages of these methods are the high cost of the initial reagents, the need to use aggressive and toxic reagents (phosgene, ammonium azide), and the complexity of the hardware design for the reactors. We have developed the highly efficient oxidative cyclocarbonylation of 2-aminophenol to oxazolidin-2-one using $FeCl_3$*$6H_2O$ and $Fe(acac)_3$ as catalysts under relatively mild conditions (100–120 °C) in the presence of CCl_4 and water. We assume that in situ-formed carbon dioxide is involved in a cyclization reaction with o-aminophenol to form the target 2-benzoxazole. The reaction takes 2–10 h to give 2-benzoxazolone a high yield.

Keywords: 2-benzoxazolone; oxazolidin-2-one; iron catalysis; heterocyclization; oxidative carbonylation

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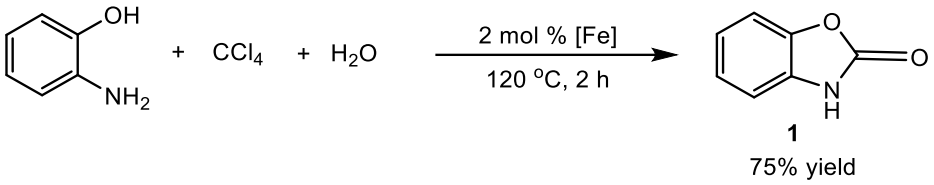
1. Introduction

2-Benzoxazolone, as well as its derivatives, are valuable structural fragments of a number of important biologically active substances. 2-Benzoxazolone derivatives are promising as antitumor [1], antimicrobial [2], antiretroviral [3], anticonvulsant [4], tranquilizing [5], and insecticidal [6] agents. 2-Benzoxazolone is usually produced by the condensation of *o*-aminophenol with urea [7], phosgene [8], and other carbonic acid derivatives. There are also methods for the synthesis of 2-benzoxazolone from salicylamide with trichloroisocyanuric acid as a chlorinating agent [9], from hydroxybenzoic acid using ammonium azide, and the Vilsmeier complex [10]. The disadvantages of these methods are the high cost of the initial reagents, the need to use aggressive and toxic reagents (phosgene, ammonium azide), and the complexity of the hardware design for the reactors.

2. Results and Discussion

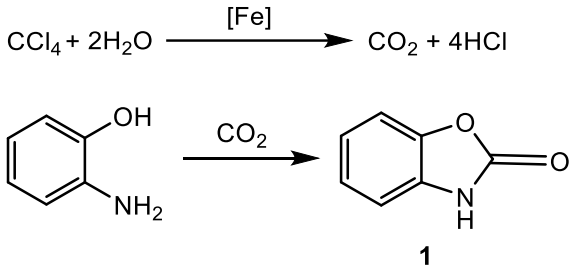
We have developed the highly efficient oxidative cyclocarbonylation of 2-aminophenol to 2-benzoxazolone **1** using $FeCl_3$*$6H_2O$ and $Fe(acac)_3$ as catalysts under relatively mild conditions (100–120 °C) in the presence of CCl_4 and water. The reaction was studied under various conditions, including the molar ratio of catalyst and reagents: [*o*-aminophenol]:[CCl_4l]:[H_2O]:[$FeCl_3$*$6H_2O$] = [50–200]:[400–7800]:[0–800]:[1–10], 100–120 °C, 0.25–10 h. A number of solvents were also tested: propanol, ethanol, 1-butanol, benzyl alcohol, ethyl acetate, toluene, and acetonitrile. The yield of 2-benzoxazolone was 75% in acetonitrile using the

following conditions: [*o*-aminophenol]:[CCl_4l:[H_2O]:[$FeCl_3$*$6H_2O$] = 50:400:800:1, 120 °C, 2 h (Scheme 1). The reaction was carried out in a micro-autoclave (ampoule with stirring). Carrying out the reaction in an open system using microwave irradiation made it possible to reduce the reaction time to 30 min; however, the yield of 2-benzoxazolone did not exceed 40%. The structure of 2-benzoxazolone was established by ^1H, ^{13}C NMR spectroscopy, infrared spectroscopy, and GC-MS, as well as a comparison with the literature data [11]:



Scheme 1. The preparation of 2-benzoxazolone **1**.

We assume that carbon dioxide and hydrogen chloride are formed in situ under the reaction conditions, similarly to [12]. Then, CO_2 reacts to o-aminophenol to give the target benzoxazolone (Scheme 2).



Scheme 2. Mechanism of 2-benzoxazolone **1** synthesis.

The formation of carbon dioxide was confirmed by GC-MS. According to the weather observatory on Mauna Loa in May 2022, the maximum concentration of CO_2 in the atmosphere was 0.042% (420.99 ppm) [13]. In the sample we analyzed, there was 12.5 times more carbon dioxide than in the atmosphere (Figure 1).

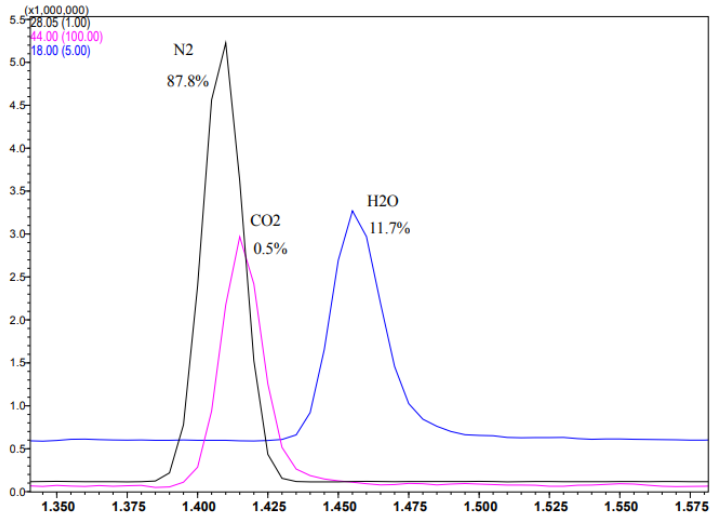


Figure 1. Data from the mass spectrum of the gas phase of the reaction mixture.

It should be noted that the introduction of Et_3N into the reaction reduces the yield of 2-benzoxazole by 25%. Et_3N "binds" to the HCl formed during the reaction, so we do not exclude the role of acid catalysis.

3. Conclusions

Thus, we developed a method to produce 2-benzoxazolone from *o*-aminophenol and carbon tetrachloride in the presence of iron-containing catalysts.

4. Experimental Part

o-Aminophenol, carbon tetrachloride (Aldrich), $FeCl_3$*$6H_2O$, and $Fe(acac)_3$ (Acros) were commercial reagents. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-II 400 Ascend instrument (400 MHz for ^1H and 100 MHz for^{13}C in $CDCl_3$). Mass spectra were run on a Shimadzu GCMS-QP2010Plus mass spectrometer (SPB-5 capillary column, 30 m × 0.25 mm, helium as the carrier gas, temperature programming from 40 to 300 °C at 8 °C/min, the evaporation temperature of 280 °C, ion source temperature of 200 °C, and ionization energy of 70 eV). The course of the reaction and the purity of the products were monitored by gas-liquid chromatography on a Shimadzu GC-9A, GC-2014 instrument [2 m × 3 mm column, SE-30 silicone (5%) on Chromaton N-AW-HMDS as the stationary phase, with temperature programming from 50 to 270 °C at 8 °C/min, helium as the carrier gas (47 mL/min)].

4.1. Method A

The reaction was carried out in a glass ampoule (V = 10 mL) placed in a stainless-steel micro-autoclave (V = 17 mL) under controlled heating with stirring. $FeCl_3$*$6H_2O$, *o*-aminophenol, CCl_4, and H_2O at a molar ratio [*o*-aminophenol]:[CCl_4l:[H_2O]:[$FeCl_3$*$6H_2O$] = 50:400:800:1 were loaded into the ampoule. The sealed ampoule was placed in an autoclave, which was hermetically sealed. The reaction was carried out at 100–120 °C for 2–10 h. After the completion of the reaction, the ampoule was opened, the reaction mixture was neutralized with dry $NaHCO_3$, impurities were purified by chromatography (SiO_2, eluent—ethyl acetate), and the solvents were distilled off on a rotary evaporator.

4.2. Method B

The synthesis of benzoxazolone was carried out in a round bottom flask equipped with a reflux condenser in a microwave oven with a power of 600 watts at 120 °C for 30 min. The reaction proceeded under constant stirring (built-in magnetic stirrer). After the completion of the synthesis, the reaction mixture was treated similarly to Method A.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Turanl, S.; Uslu, A.G.; Ödemi, A. Synthesis of Novel Potential ROCK Inhibitors and Their Antimigratory Effects. *Org. Commun.* **2020**, *13*, 165–174. [CrossRef]
2. Zheng, Z.; Parsons, J.B.; Tangallapally, R.; Zhang, W.; Rock, C.O.; Lee, R.E. Discovery of Novel Bacterial Elongation Condensing Enzyme Inhibitors by Virtual Screening. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2585–2588. [CrossRef] [PubMed]
3. Safakish, M.; Hajimahdi, Z.; Zabihollahi, R.; Aghasadeghi, M.R.; Vahabpour, R.; Zarghi, A. Design, Synthesis, and Docking Studies of New 2-Benzoxazolinone Derivatives as Anti-HIV-1 Agents. *Med. Chem. Res.* **2017**, *26*, 2718–2726. [CrossRef]
4. Bywater, B.W.G.; Coleman, W.R.; Kamm, O.; Merritt, H.H.; Merritt, H. Synthetic Anticonvulsants and Pharmacology. *Prelim. Anticonvuls.* **1945**, *27*, 4–6.
5. Ceccarelli, S.M.; Jaeschke, G.; Buettelmann, B.; Huwyler, J.; Kolczewski, S.; Peters, J.U.; Prinssen, E.; Porter, R.; Spooren, W.; Vieira, E. Rational Design, Synthesis, and Structure-Activity Relationship of Benzoxazolones: New Potent Mglu5 Receptor Antagonists Based on the Fenobam Structure. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1302–1306. [CrossRef] [PubMed]
6. Maag, D.; Dalvit, C.; Thevenet, D.; Köhler, A.; Wouters, F.C.; Vassao, D.G.; Gershenzon, J.; Wolfender, J.L.; Turlings, T.C.J.; Erb, M.; et al. 3-β-d-Glucopyranosyl-6-Methoxy-2-Benzoxazolinone (MBOA-N-Glc) Is an Insect Detoxification Product of Maize 1,4-Benzoxazin-3-Ones. *Phytochemistry* **2014**, *102*, 97–105. [CrossRef] [PubMed]
7. Pena-Lopez, M.; Neumann, H.; Beller, M. (Enantio)Selective Hydrogen Autotransfer: Ruthenium-Catalyzed Synthesis of Oxazolidin-2-Ones from Urea and Diols. *Angew. Chem. Int. Ed.* **2016**, *55*, 7826–7830. [CrossRef] [PubMed]
8. Vo, L.; Ciula, J.; Gooding, O.W. Chemical Development on the Chiral Auxiliary (S)-4-(Phenylmethyl)-2-Oxazolidinone Utilizing Automated Synthesis and DoE. *Org. Process Res. Dev.* **2003**, *7*, 514–520. [CrossRef]
9. Gambacorta, G.; Baxendale, I.R. Continuous-Flow Hofmann Rearrangement Using Trichloroisocyanuric Acid for the Preparation of 2-Benzoxazolinone. *Org. Process Res. Dev.* **2022**, *26*, 422–430. [CrossRef]
10. Sridhar, R.; Perumal, P.T. A Novel Method for the Synthesis of 2 (3 H)-Benzimidazolones, 2 (3 H)-Benzoxazolone, and 2 (3 H)-Benzothiazolone via In Situ Generated Ortho Substituted Benzoic Acid Azides: Application of Ammonium Azide and Vilsmeier Complex for Acid Azide Generation. *Synth. Commun.* **2004**, *34*, 735–742. [CrossRef]
11. Prasanthi, A.V.G.; Begum, S.; Srivastava, H.K.; Tiwari, S.K.; Singh, R. Iron-Catalyzed Arene C-H Amidation Using Functionalized Hydroxyl Amines at Room Temperature. *ACS Catal.* **2018**, *8*, 8369–8375. [CrossRef]
12. Khusnutdinov, R.I.; Bayguzina, A.R.; Asylbaeva, R.S.; Aminov, R.I.; Dzhemilev, U.M. Synthesis of N-arylsubstituted pyrrolidines and piperidines by reaction of anilines with α,ω-diols catalyzed by $FeCl_3.6H_2O$ in carbon tetrachloride. *ARKIVOC* **2014**, *341*, 350.
13. National Oceanic and Atmospheric Administration. Carbon Dioxide Now More Than 50% Higher Than Pre-Industrial Levels. Available online: https://www.noaa.gov/ (accessed on 15 September 2022).