Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Synthesis of benzoxazoles *via* a silver mediated oxidation

Chloe D. Wong, Kimiya Ganjooi, Maetja Verbarendse, Jessica M. Travis, Mark H. S. Troftgruben, Hannah R. Mora, Isabella Oldenburg, Robert Lammert Jr., Horacio Lazaro & Scott Eagon

To cite this article: Chloe D. Wong, Kimiya Ganjooi, Maetja Verbarendse, Jessica M. Travis, Mark H. S. Troftgruben, Hannah R. Mora, Isabella Oldenburg, Robert Lammert Jr., Horacio Lazaro & Scott Eagon (2023) Synthesis of benzoxazoles *via* a silver mediated oxidation, Synthetic Communications, 53:1, 32-39, DOI: 10.1080/00397911.2022.2148223

To link to this article: https://doi.org/10.1080/00397911.2022.2148223

© 2022 The Author(s). Published with license by Taylor & Francis Group, LLC.

View supplementary material

Published online: 22 Nov 2022.

Submit your article to this journal

Article views: 725

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=lsyc20

SYNTHETIC COMMUNICATIONS®
2023, VOL. 53, NO. 1, 32–39
https://doi.org/10.1080/00397911.2022.2148223

Taylor & Francis
Taylor & Francis Group

OPEN ACCESS Check for updates

Synthesis of benzoxazoles *via* a silver mediated oxidation

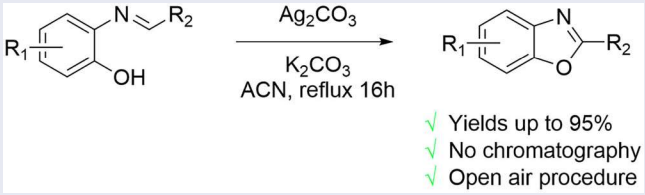
Chloe D. Wong[a], Kimiya Ganjooi[a], Maetja Verbarendse[a], Jessica M. Travis[a], Mark H. S. Troftgruben[a], Hannah R. Mora[a], Isabella Oldenburg[a], Robert Lammert, Jr.[a], Horacio Lazaro[b], and Scott Eagon[a]

[a]Department of Chemistry & Biochemistry, California Polytechnic State University, San Luis Obispo, CA, USA; [b]Promega Biosciences, San Luis Obispo, CA, USA

ABSTRACT

A silver carbonate-based method to synthesize benzoxazoles from imines has been developed. The reaction is extremely mild, tolerates several heterocycles and functional groups, and provides highly functionalized benzoxazoles in modest to good yields. The reaction proceeds in an array of solvents and atmospheric conditions, demonstrating the robustness of this oxidation method and its ability to provide an alternative method for the easy preparation and isolation of these bioactive compounds.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 13 August 2022

KEYWORDS
Benzoxazoles; oxidation; silver carbonate

Introduction

The benzoxazole moiety has conferred promising therapeutic effects in a variety of applications due to its biological activity within the body. Studies have described various therapeutic drugs with this shared pharmacophore that serve as antiviral, antifungal, antibiotic, and anticancer agents.[1] Benzoxazoles in particular are known for their ability to inhibit kinases, including CLK1[2] and VEGFR2.[3] Given this range of biological activity, many researchers continue to prepare a series of substituted benzoxazoles to produce new treatments for a broad spectrum of human diseases.

Several methods have been developed to synthesize benzoxazole compounds, with most methods involving the oxidative cyclization of phenolic imines generated *in situ* from the condensation of 2-aminophenols and aldehydes. For example, Cao et al. reported in 2010 that an iron-catalyzed coupling reaction of 2-aminophenols and

CONTACT Scott Eagon seagon@calpoly.edu Department of Chemistry & Biochemistry, California Polytechnic State University, San Luis Obispo, CA 93407, USA.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/00397911.2022.2148223

© 2022 The Author(s). Published with license by Taylor & Francis Group, LLC.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

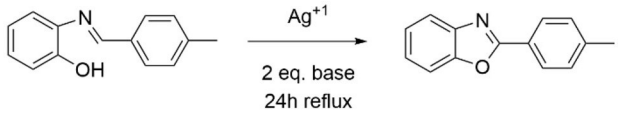
benzaldehydes affords substituted aryl benzoxazoles.[4] While this reaction tolerated an array of substrates and led to highly substituted benzoxazoles, it required an oxygen atmosphere and flash chromatography purification. Alternatively, Kawashita et al. developed a method without the usage of metal oxides by instead using an oxygen atmosphere and activated charcoal.[5] This reaction is complete in 4 h with the addition of heat, but column chromatography is required to isolate pure product and only a handful of functional groups are reported. More recently, Cho et al. reported a cyanide-based cyclization and oxidation of imines producing benzoxazoles compounds in high yield.[6] However, the nucleophilic nature of the cyanide oxidizer limited the functional group tolerability and again column chromatography was necessary for the purification and isolation of the products.

Results and discussion

Our lab became interested in the synthesis of benzoxazoles as potential inhibitors of casein kinase 2 (CK2), which is upregulated in several cancers.[7] The overexpression of CK2 has been tied to cancer development due to its role in inducing transcription factors and upregulating processes including cell proliferation, survival, migration, and inflammation, all of which are vital markers of cancer cells.[8] Since we were interested in preparing several dozen benzoxazole inhibitors with a wide range of functionality, we searched for a suitably mild cyclization/oxidation strategy. We first attempted to utilize the previously reported charcoal/O_2 method[5] but we were unable to obtain the reported yields with more diversely substituted benzoxazoles. We also attempted to reproduce a reported method that used iodine as the oxidizing agent[9] but again we were unable to achieve the reported yields with our substituted benzoxazoles. Given these issues, we decided to see if we could develop an alternative oxidation method that was mild enough to tolerate a broader range of functional groups. We previously discovered that silver salts could be used in the cyclization/oxidation of tetrahydro-β-carbolines to obtain β-carbolines without the need for purification by chromatography[10] and were curious if we could use silver salts again to prepare our desired benzoxazoles. Our resultant studies using the imine formed by the condensation of 2-aminophenol with *p*-tolualdehyde as a model compound are detailed in Table 1.

We began by utilizing the same procedure we previously optimized for the oxidation of tetrahydro-β-carbolines, which was to reflux a DMF solution containing 2 eq. of silver carbonate and lithium carbonate for 24 h.[10] We were pleasantly surprised to find that an aliquot of the final reaction mixture indicated full conversion to the product by ^{1}H NMR (Table 1, Entry 1). We next tested whether other available silver salts could also give product after an overnight reflux, finding that both silver oxide and silver chloride provided full conversion to product, but that silver nitrate gave a complex mixture of byproducts (Table 1, Entries 2–4). We decided to use silver carbonate for subsequent reactions since it is the most inexpensive commercially available silver salt. We then tested other solvents, finding that both protic and aprotic solvents (even water) provided the product in full conversion, although the reaction proceeds very slowly in water likely due to the poor solubility of the imine starting material (Table 1, Entries 5–8). We also investigated the role of atmospheric oxygen and light in the presence of

Table 1. Investigations of the silver-mediated preparation of 2-(4-methylphenyl)-1,3-benzoxazole.

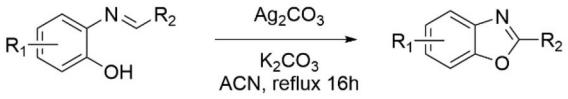


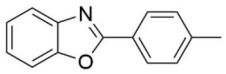
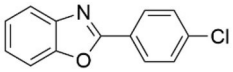
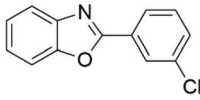
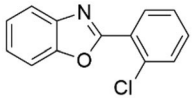
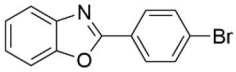
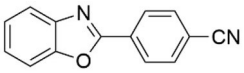
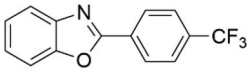
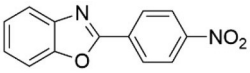
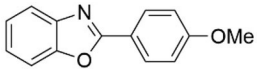
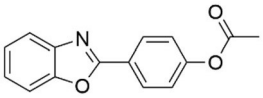
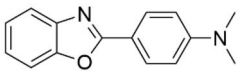
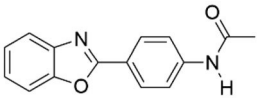
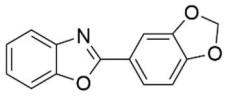
Entry	Silver salt	Base	Solvent	Atm.	Conversion[a] (%)
1	2 eq. Ag_2CO_3	Li_2CO_3	DMF	Air	100
2	2 eq. Ag_2O	Li_2CO_3	DMF	Air	100
3	2 eq. AgCl	Li_2CO_3	DMF	Air	100
4	2 eq. $AgNO_3$	Li_2CO_3	DMF	Air	–[b]
5	2 eq. Ag_2CO_3	Li_2CO_3	ACN	Air	100
6	2 eq. Ag_2CO_3	Li_2CO_3	DCM	Air	100
7	2 eq. Ag_2CO_3	Li_2CO_3	^{i}PrOH	Air	100
8[c]	2 eq. Ag_2CO_3	Li_2CO_3	H_2O	Air	100
9	2 eq. Ag_2CO_3	Li_2CO_3	DMF	Argon	100
10	2 eq. Ag_2CO_3	Li_2CO_3	DMF	O_2	100
11	2 eq. Ag_2CO_3	Li_2CO_3	DMF	Air[d]	100
12	None	None	DMF	Air	15
13	None	Li_2CO_3	DMF	Air	56
14	None	Li_2CO_3	DMF	O_2	80
15	1 eq. Ag_2CO_3	Li_2CO_3	DMF	Air	100
16	0.5 eq. Ag_2CO_3	Li_2CO_3	DMF	Air	84
17	1 eq. Ag_2CO_3	K_2CO_3	ACN	Air	100
18	1 eq. Ag_2CO_3	None	ACN	Air	59

[a]Calculated by ^{1}H NMR.
[b]Complex mixture of byproducts observed.
[c]Reaction requires 5D reflux to reach completion.
[d]Reaction run in the dark.

silver carbonate, finding that the reaction proceeds to full completion in both an argon and pure oxygen atmosphere, as well as in a flask open to the air in the dark (Table 1, Entries 9–11). In the absence of silver, the reaction still partially proceeds in an open-air flask with faster conversion observed when the base is present (Table 1, Entries 12 and 13). Moreover, the reaction proceeds to 80% completion in a pure oxygen atmosphere in the absence of silver (Table 1, Entry 14). These results indicate that both oxygen gas and Ag^{+} salts contribute to product formation. The role of silver in the oxidation process is also supported by the fact that a silver mirror is sometimes observed in the product flask (while other times small nuggets of silver metal are obtained). Given the increased risk of fires and explosions when utilizing a pure oxygen atmosphere, we opted to continue to use an open-air flask procedure. Since atmospheric oxygen contributes to product formation, we tried smaller equivalents of Ag_2CO_3 and found that 1 eq. provided full conversion after an overnight reflux, but that 0.5 eq. only gave slightly more than half conversion to product (Table 1, Entries 15 and 16). Given our results, we decided to use 1 eq. of Ag_2CO_3 in acetonitrile in an open-air flask. We selected acetonitrile due to its lower boiling point compared to DMF, making it easier to remove under reduced pressure. We also found that switching to the less expensive K_2CO_3 instead of Li_2CO_3 afforded full conversion to product, but that the base is still required for full conversion (Table 1, Entries 17 and 18). We believe it is feasible that fewer equivalents of Ag_2CO_3 could likely be used in a pure oxygen atmosphere, but we decided to avoid this method due to the safety concerns mentioned previously. While some additional questions remain, such as a better understanding of the kinetics and

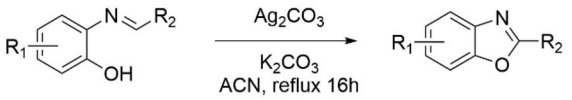
Table 2. Synthesis of substituted benzoxazoles using Ag_2CO_3.

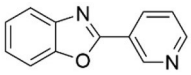
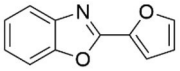
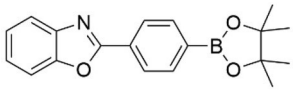
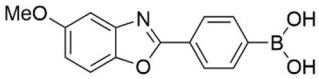
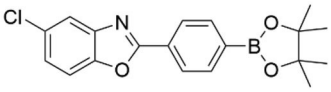


Entry	Product	Isolated yield (%)
1		84
2		77
3		95
4		87
5		26
6		39
7		71
8		23
9		87
10		58
11		84
12		61
13		87

(*continued*)

Table 2. Continued.



Entry	Product	Isolated yield (%)
14		69
15		71
16		88
17		47
18		31

mechanism of this reaction, we decided that our procedure was sufficiently optimized for our purposes and decided to move on to investigate the substrate scope for this novel reaction.

With our optimized procedure in hand, we then tested a variety of substituted benzoxazoles as shown in Table 2. Reactions were performed on a 2 mmol scale and the product was isolated using only a series of filtrations to remove the unwanted salts (see Supporting Information).

This procedure was highly tolerant of a wide variety of functional groups and yields ranged from modest to very good (23–95%). Halide, alkyl, and electron-rich substitutions generally provided the best yields (Table 2, Entries 1–4, 9, and 11), while cyano, nitro, and bromo-substituted benzoxazoles were isolated with the lowest observed yields (Table 2, Entries 5, 6, and 8). Interestingly, a trifluoromethyl-substituted benzoxazole was isolated in 71% yield (Table 2, Entry 7) in contrast to the low yields observed for benzoxazoles with other electron-withdrawing substituents. Benzoxazoles bearing heterocycles were readily obtained with this method, with a 1,3-benzodioxole, pyridine and furan substituted benzoxazoles obtained in good yields. Since our group was interested in some possible coupling chemistry, we also investigated a selection of boronic acid and pinacol borane substitutions and were pleased to see that they were also tolerated by this synthetic method, providing the product benzoxazoles in 31–88% yields (Table 2, Entries 16–18).

Conclusion

The synthesis of substituted benzoxazoles from the corresponding imines using Ag_2CO_3 is a new way to prepare these synthetically and biologically useful compounds. Products

are readily isolated by a simple filtration method without the need for chromatography or a pure oxygen atmosphere after refluxing the reaction solvent overnight in the presence of an excess carbonate base. While a handful of substitutions provided the product in modest yields, this method tolerates a wide range of functionality including halides, esters, amides, ethers, boronic acids, and pinacol boronates. Moreover, the reaction can be run in a variety of solvents—both protic and aprotic. In conclusion, this method provides an exceptionally mild alternative for the preparation of substituted benzoxazoles.

Experimental

General information

^{1}H and ^{13}C and Nuclear Magnetic Resonance (NMR) spectra were obtained on a 300 or 400 MHz instrument using $CDCl_3$ as the solvent. Chemical shifts were reported as δ values in parts per million (ppm) relative to the solvent. All reactions were performed open to the atmosphere unless indicated otherwise. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 250 μm layer silica plates visualized with either 254 or 365 nm wavelengths. Sonication was performed in an Ultrasonic Cleaner GB928. All melting points are uncorrected. All solvents were used without purification and no attempts were made to exclude atmospheric moisture unless indicated otherwise in the following procedures. Glassware was dried for at least 1 h in a 90 °C oven before use. FT-IR was obtained using a Nicolet iS5. HRMS was determined using an LCMS system consisting of a Shimadzu Prominence UFLC with LC-20ADXR pumps, SIL-20AXR autosampler, CTO-20AC column oven, and SPD-M20A DAD detector. All HRMS samples were prepared at 1 mg/mL in MeOH, then diluted 1:20 in MeOH for testing with 2 μL injection volume, and mass was detected with an ABSciex TripleTOF 5600+ with CDS (Calibrant Delivery System) and DuoSpray Ion Source in positive ionization mode.

General procedure for the synthesis of imines

Following a previously reported procedure,[11] 5.0 mmol of the aminophenol (1 eq.) and 5.0 mmol of aldehyde (1 eq.) are dissolved in 17 mL of DCM, giving a 0.30 M solution, in a round-bottomed flask equipped with a stir bar. The solution is gently stirred, then a large excess (3.3 g) of either $MgSO_4$ or Na_2SO_4 is added to the mixture. The flask is capped with a septum to prevent evaporation and allowed to stir. The reaction is monitored by either TLC or by taking an ^{1}H NMR of an aliquot of the solution. Most substrates are complete in 1–3 days, although some substrates can take 7–10 days. Once the reaction is complete, the solution is filtered to remove the solids, and the filtrate is concentrated under reduced pressure using a rotary evaporator to obtain the product. Products were confirmed to have >95% purity by ^{1}H NMR and were used without further purification.

General silver-mediated preparation of benzoxazoles

On a 2.0 mmol scale, 1 eq. of imine (2.0 mmol), 1 eq. of Ag_2CO_3 (0.55 g, 2.0 mmol), and 2 eq. of K_2CO_3 (0.55 g, 4.0 mmol) are placed in a round bottom flask equipped with a

stir bar. Twenty milliliters of acetonitrile is then added and the mixture is gently stirred. A condenser is attached to the top of the flask and the mixture is refluxed for 16 h. As the reaction proceeds, the mixture often takes on a dark, metallic color and either a silver mirror or silver nuggets appear in the flask. Once the reaction is confirmed complete by TLC, the crude mixture is first filtered through a course-fritted filter to remove the solids. The reaction flask is then washed 2× with 5–10 mL of acetonitrile and this solvent is poured through the same fritted filter to also wash the captured solids, combining the organic layers. These combined acetonitrile layers are then filtered a second time, this time through a fine fritted filter. This twice-filtered solution is then evaporated under reduced pressure using a rotary evaporator to obtain the crude product, often as a dark solid. The flask holding the crude solid is filled with D. I. water, and the crude product is dispersed into the water with a spatula and/or sonication. Once the product has been fully suspended in the water as a heterogenous mixture, this solution is filtered through a Buchner funnel to capture the solid. Alternatively, the combined twice-filtered acetonitrile solution can be slowly dripped into a beaker holding a large volume of stirring D.I. water (∼250 mL) to precipitate out the product, which can be captured using a Buchner filter as previously discussed. The captured solid is washed 2× more with D.I. water and drying the isolated solid provides the final compound. Yield and characterization data for all compounds are provided in the Supporting Information document.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This material is based upon work supported by the National Science Foundation under Grant Number NSF-1952691, as well as support from the Bill and Linda Frost Fund at California Polytechnic State University.

References

[1] Kamal, U.; Javed, N. M.; Arun, K. Biological Potential of Benzoxazole Derivatives: An Updated Review. *Asian J. Pharm. Clin. Res.* **2022**, *13*, 1–14. DOI: 10.22159/ajpcr.2020.v13i8.37958.

[2] Murar, M.; Dobias, J.; Sramel, P.; Addova, G.; Hanquet, G.; Bohac, A. Novel CLK1 Inhibitors Based on *N*-Aryloxazole-2-Amine Skeleton – A Possible Way to Dual VEGFR2 TK/CLK Ligands. *Eur. J. Med. Chem.* **2017**, *126*, 754–761. DOI: 10.1016/j.ejmech.2016.11.003.

[3] Vojtickova, M.; Dobias, J.; Hanquet, G.; Addova, G.; Cetin-Atalay, R.; Yildirim, D. C.; Bohac, A. Ynamide Click Chemistry in Development of Triazole VEGFR2 TK Modulators. *Eur. J. Med. Chem.* **2015**, *103*, 105–122. DOI: 10.1016/j.ejmech.2015.08.012.

[4] Cao, K.; Tu, Y.; Zhang, F. Synthesis of Substituted Benzoxazoles by the Iron(III)-Catalyzed Aerobic Oxidation Process. *Sci. China Chem.* **2010**, *53*, 130–134. DOI: 10.1007/s11426-010-0027-x.

[5] Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. Direct and Practical Synthesis of 2-Arylbenzoxazoles Promoted by Activated Carbon. *Org. Lett.* **2003**, *5*, 3713–3715. DOI: 10.1021/ol035393w.

[6] Cho, Y.; Lee, C.; Cheon, C. Cyanide as a Powerful Catalyst for Facile Synthesis of Benzofused Heteroaromatic Compounds via Aerobic Oxidation. *Tetrahedron* **2013**, *69*, 6565–6573. DOI: 10.1016/j.tet.2013.05.138.

[7] Chua, M. M. J.; Ortega, C. E.; Sheikh, A.; Lee, M.; Abdul-Rassoul, H.; Hartshorn, K. L.; Dominguez, I. CK2 in Cancer: Cellular and Biochemical Mechanisms and Potential Therapeutic Target. *Pharmaceuticals* **2017**, *10*, 18. DOI: 10.3390/ph10010018.

[8] Litchfield, D. W. Protein Kinase CK2: Structure, Regulation and Role in Cellular Decisions of Life and Death. *Biochem. J.* **2003**, *369*, 1–15. DOI: 10.1042/bj20021469.

[9] Osowska, K.; Miljanic, O. S. Oxidative Kinetic Self-Sorting of a Dynamic Imine Library. *J. Am. Chem. Soc.* **2011**, *133*, 724–727. DOI: 10.1021/ja109754t.

[10] Durham, S. D.; Sierra, B.; Gomez, M. J.; Tran, J. K.; Anderson, M. O.; Whittington-Davis, N. A.; Eagon, S. Synthesis of *β*-Carbolines via a Silver-Mediated Oxidation of Tetrahydro-*β*-Carbolines. *Tetrahedron Lett.* **2017**, *58*, 2747–2750. DOI: 10.1016/j.tetlet.2017.05.098.

[11] Das, T. K.; Mondal, S.; Gonnade, R. G.; Biju, A. T. Base-Free and Catalyst-Free Synthesis of Functionalized Dihydrobenzoxazoles via Vinylogous Carbonate to Carbamate Rearrangement. *Org. Lett.* **2017**, *19*, 5597–5600. DOI: 10.1021/acs.orglett.7b02733.