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Eco-Friendly Synthesis of 2-Styryl-benzo[*d*][1,3]oxazin-4-ones from *N*-Cinnamoyl-Anthranilic Acids

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Abstract

N-cinnamoyl anthranilic acids are synthesized in a single, eco-friendly step by condensing various cinnamic acids with free 2-aminobenzoic acid derivatives using the mixed carbonic anhydride method. Subsequently, converting the resulting *N*-cinnamoyl anthranilic acids into their corresponding mixed carbonic anhydrides rapidly and efficiently affords 2-styryl-benzo[*d*][1,3]oxazin-4-ones. The method employs green solvents, such as acetone and 2-methyltetrahydrofuran; does not require metal catalysts or reflux conditions; and yields the desired final products without chromatographic purification.

Keywords: benzo[*d*][1,3] oxazin-4-ones; anthranilic acids; hydroxycinnamic acids

1. Introduction

The 4H-benzo[*d*][1,3]oxazin-4-one scaffold is a highly versatile and essential heterocyclic system in organic and medicinal chemistry [1–3]. This fused bicyclic framework—featured in several natural and bioactive compounds, including cetilistat, an anti-obesity drug [4]—contains a 1,3-oxazine ring fused to a benzene ring and has attracted sustained scientific interest due to its broad range of applications [5].

These include its use as a key synthetic intermediate and as a core pharmacophore in biologically active molecules (Figure 1). The importance of the benzo[1,3]oxazin-4-one core is twofold. First, it serves as a crucial starting point for the synthesis of numerous nitrogen-containing heterocycles. Its reactivity—driven by ring strain and the electrophilic nature of carbonyl carbon—enables facile ring-opening reactions with various nucleophiles, particularly amines [6].

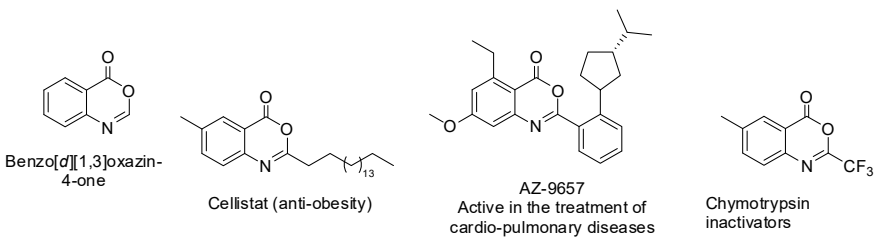

Figure 1. Representative examples of biologically relevant compounds featuring the benzo[*d*][1,3]oxazin-4-one heterocyclic core.

This transformation efficiently provides 2-aminobenzamide derivatives, which are essential precursors for the synthesis of several medicinally relevant scaffolds, including quinazolinones, quinazolines, and benzodiazepines. Notably, this synthetic pathway is fundamental for the preparation of several blockbuster anticancer agents [7].

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Beyond its role as a synthetic building block, the benzo[1,3]oxazin-4-one framework—especially when functionalized at C2—can undergo further modification via C-H activation at the 2-position [8,9]. Derivatives of this kind have demonstrated antimicrobial, anticancer, anti-inflammatory, and antiviral properties, making them attractive candidates in drug discovery [10]. 2-Styryl-substituted benzoxazinones have emerged as a promising new scaffold for rhomboid protease inhibitors [11].

Given this broad utility, the development of efficient, scalable synthetic methods for constructing the 4H-benzo[*d*][1,3] oxazin-4-one scaffold remains critically important.

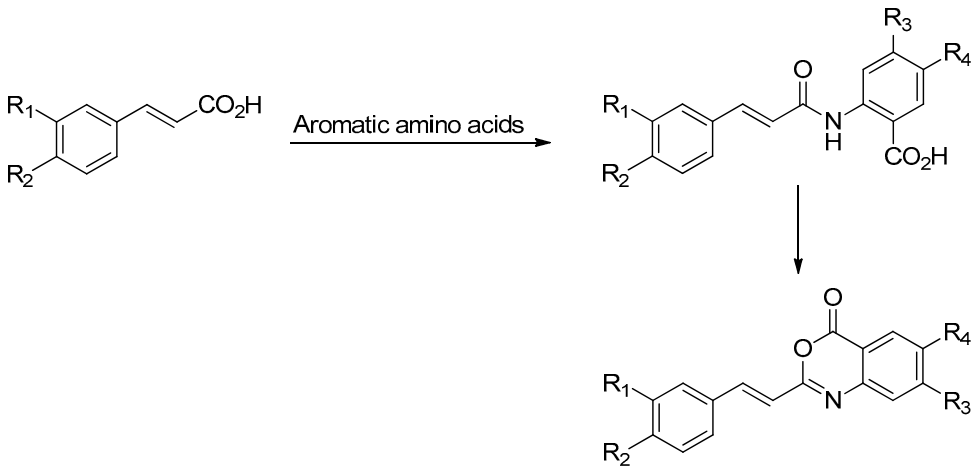
Nonetheless, current research continues to investigate innovative approaches—such as solid-phase synthesis, microwave-assisted protocols, and sustainable catalytic systems—to improve yields, reduce reaction times, and enhance functional-group tolerance [12].

Recently, 2-substituted-4H-benzo[*d*][1,3]oxazin-4-ones have been synthesized from substituted anthranilic acids through decarboxylative coupling with α-ketoacids, catalyzed by cuprous salts [13]. These processes are typically carried out in DMF, require prolonged heating at 55 °C, and necessitate chromatographic purification. Alternatively, condensation between ortho-ester and substituted anthranilic acids under thermal or microwave conditions yields benzo[*d*][1,3]oxazin-4-ones in moderate yield, along with the corresponding 1,2-dihydro-4H-benzoxazine-4-ones [14].

An oxidative coupling between substituted anthranilic acids and isocyanides, mediated by the I_2-*t*-butyl hydroperoxide system, affords another class of 2-aminobenzoxazin-4-ones, though typically in modest yields and highly dependent on the substitution pattern of the anthranilic region [15]. Improved results can be achieved with the addition of palladium catalysts, but at the expense of sustainability [16].

Many of these methods rely on toxic reagents and solvents, generate hazardous waste, and demand high energy input—conditions that conflict with the fundamental principles of green chemistry. As the chemical industry faces growing pressure to adopt sustainable practices, the development of environmentally benign synthetic protocols has become not merely desirable but imperative. In recent years, this challenge has stimulated extensive research focused on greening the synthesis of numerous heterocyclic systems [17].

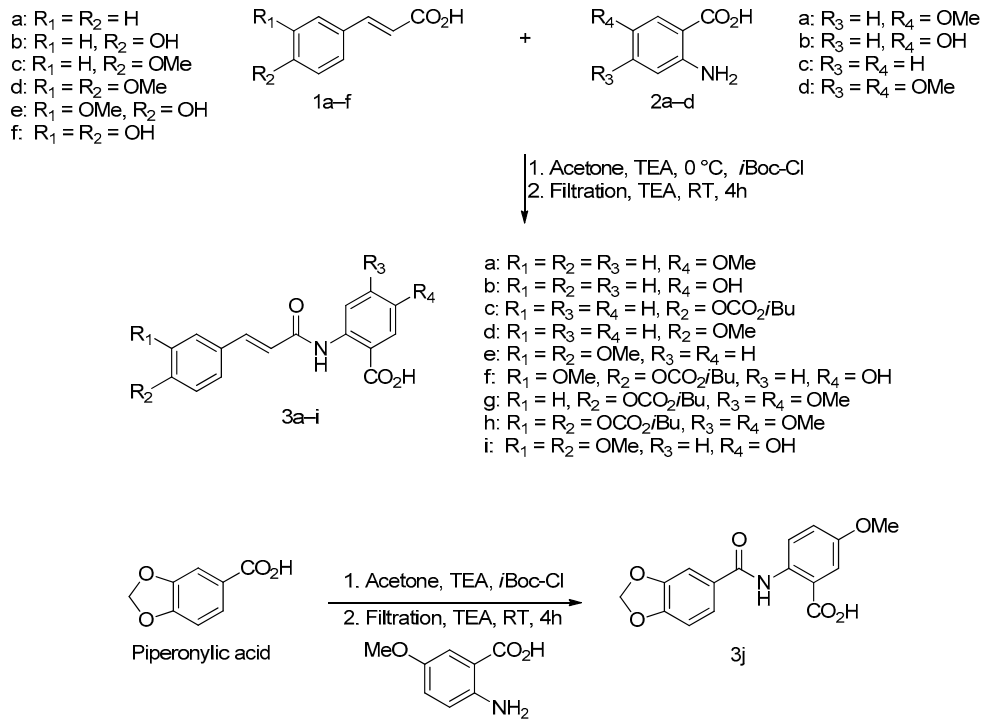
This paper focuses specifically on new, simplified, and increasingly eco-friendly methodologies for constructing the 2-styryl-substituted 4H-benzo[*d*][1,3]oxazin-4-one scaffold from readily available *N*-cinnamoyl-anthranilic acids (Scheme 1). We evaluate green synthetic approaches as a framework for assessing the sustainability of these new protocols. By integrating this perspective with our previous experience on *N*-cinnamoyl anthranilic acids [18], we aim to develop a safer, cleaner, and more sustainable route to this valuable heterocycle, thereby aligning synthetic chemistry with modern eco-friendly objectives.



Scheme 1. 2-Styryl-benzo[*d*][1,3]oxazin-4-ones from *N*-cinnamoyl-anthranilic acids.

2. Results and Discussion

The activation and simultaneous protection of common hydroxycinnamic acids (HCAs) using the triethylamine–isobutyl chloroformate reagent system in eco-friendly solvents such as water, ethyl acetate, and acetone has enabled the development of an environmentally friendly platform for synthesizing a wide array of HCA derivatives, including amides, esters, and alcohols, several of which occur in natural products [19,20]. Coupling activated HCAs with aromatic amino acids has further enabled the development of a green synthetic route to natural avenanthramides and numerous analogues [18]. In this work, a series of *N*-cinnamoyl anthranilic acids was quickly prepared in acetone using the triethylamine–isobutyl chloroformate system. Coupling reactions with free amino acids cannot take place in water, the most well-known green solvent, because the aqueous phase contains large amounts of ammonium salts formed during the activation and protection of hydroxycinnamic acids [21], which prevent the existence of an unprotonated amino group. After activation and/or protection of the various cinnamic acids 1a–f at 0 °C, the reaction mixture was filtered, and the resulting filtrate was directly added to the aromatic amino acid 2a–d, along with an additional equivalent of triethylamine, as shown in Scheme 2.



Scheme 2. Preparation of *N*-cinnamoyl and *N*-benzoyl-anthranilic acids.

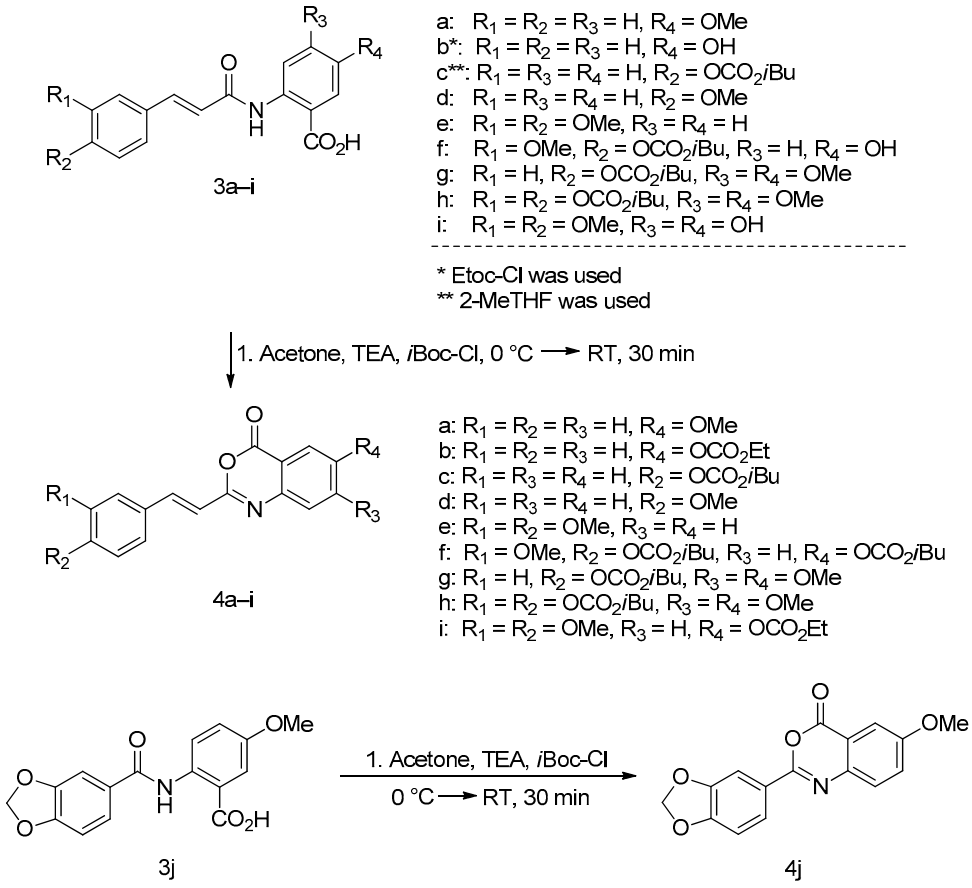
The reaction mixture, stirred for 4 h at room temperature, was evaporated in vacuo, and the resulting residue was treated with anhydrous ethyl ether and stirred for an additional hour. This step ensures complete precipitation of the amide product, while unreacted starting materials remain in solution. The precipitated solid was collected by filtration and subsequently crystallized from an ethyl acetate–hexane mixture. Under these conditions, *N*-cinnamoyl anthranilic acids 3a–3i were obtained in 72–93% yields without the need for chromatographic purification (Scheme 2). Aromatic amino acids 2a, 2b, and 2d provided higher yields than 2c, likely due to the presence of electron-donating substituents in the para position relative to the amino group, which enhances nucleophilicity.

A representative example involving a substituted benzoic acid was also examined: conjugate coupling between 5-methoxy-2-aminobenzoic acid 2a and piperonylic acid afforded the corresponding *N*-piperonyl amide 3j in 79% yield (Scheme 2).

The *N*-cinnamoyl anthranilic acids 3c, 3f, and 3h, derived from *p*-coumaric, ferulic, and caffeic acids, respectively, were obtained with the phenolic groups in the cinnamic moiety protected as carbonates. In contrast, 3b and 3f were isolated with free phenolic groups in the anthranilic portion, indicating that *O*-acylation does not occur under these reaction conditions.

During the synthesis of *N*-cinnamoyl anthranilic acids, our initial aim was to further functionalize the free carboxyl group by coupling it with a *C*-protected α-amino acid, using the mixed carbonic anhydride method. Unexpectedly, the reaction mixture did not yield the anticipated coupling product; instead a new compound was formed, which was subsequently identified as 2-styryl-substituted 4H-benzo[1,3]oxazin-4-one.

Consequently, *N*-cinnamoyl-anthranilic acids 3a–i and *N*-piperonyl-anthranilic acid 3j were activated in acetone or 2-methyltetrahydrofuran using 1.5 equivalents of the triethylamine–alkyl chloroformate reagent system at 0 °C for 15 min, as illustrated in Scheme 3.

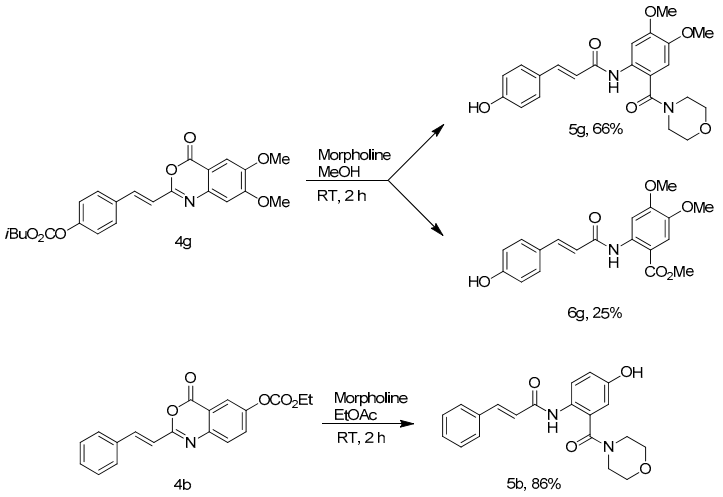


Scheme 3. Preparation of benzo[1,3]oxazin-4-ones from *N*-cinnamoyl anthranilic acids.

The 2-styryl-substituted benzo[1,3]oxazin-4-ones 4a–i and 2-(benzo[*d*][1,3]dioxol-5-yl)-6-methoxy-4H-benzo[*d*][1,3]oxazin-4-one 4j were synthesized within minutes, providing isolated yields above 90% after a simple ethyl acetate–water work-up. In this transformation, ethyl chloroformate may also be employed as an effective activating reagent. Notably, (*E*)-2-(3,4-dimethoxystyryl)-4-oxo-4H-benzo[*d*][1,3]oxazin-6-yl ethyl carbonate 4i, obtained from the 5-hydroxy analogue of Tranilast 3i, was produced in 95% overall yield through two sequential steps starting from 3,4-dimethoxycinnamic acid 1d and 5-hydroxy-2-aminobenzoic acid 2b, without any purification (see Supplementary Materials).

As illustrated for 4b and 4f in Scheme 3, the cyclization proceeds using three equivalents of the alkyl chloroformate/triethylamine reagent system and the corresponding 2-styryl-substituted benzo[1,3]oxazin-4-ones with phenol groups protected as labile carbonates on the anthranilic portion.

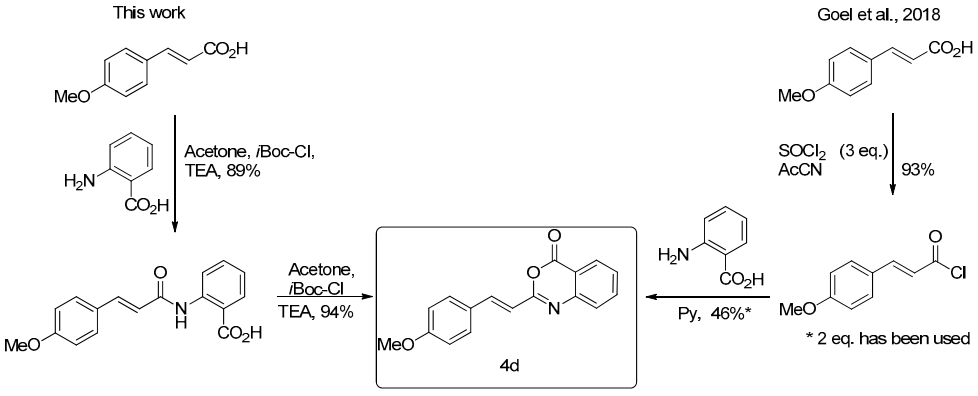
Carbonate groups on phenols can be removed within one hour by treatment with an excess of a secondary amine, such as morpholine, in methanol [18]. We therefore employed morpholine both to remove the carbonate protecting group and to induce ring opening of the benzoxazinone, affording the corresponding morpholino amide (Scheme 4).



Scheme 4. Ring opening and deprotection of 4g and 4b with morpholine, in methanol or ethyl acetate.

However, when both transformations were conducted in methanol, the reaction produced not only the expected amide with the free phenolic group but also a significant amount of the corresponding methyl ester. The product distribution confirmed the higher nucleophilicity of the secondary amine compared to a primary alcohol, even when the latter is present in large excess. In contrast, performing both processes in ethyl acetate, without methanol, at room temperature for two hours yielded the amide with the free phenolic function exclusively, in excellent yield (Scheme 4).

Finally, to evaluate the environmental impact of these processes, we compared the preparation of (*E*)-2-(4-methoxystyryl)-4H-benzo[*d*][1,3]oxazin-4-one 4d obtained from 3d using the method described here (Scheme 5), with the same compound prepared using procedures reported in the literature [11].



Scheme 5. Comparative preparation of (*E*)-2-(4-methoxystyryl)-4*H*-benzo[*d*][1,3]oxazin-4-one 4d [11].

In the literature method, the acyl chloride approach, commonly employed for the acylation of aromatic amino acids in the synthesis of avenanthramides [22], is used in substantial excess. It serves as both the acylation equivalent and the cyclization reagent through anhydride formation. In this case, the % of atom economy (AE), defined as

$$\text{AE (\%)} = 100 \times \text{Molar mass of product/Molar mass of all reactants}$$

is 52. An even larger excess is required when the aromatic amino acid also contains a phenolic group, as in the case of avenanthramides 3b and 3f. Additionally, the necessary acyl chloride must be prepared using a large excess of $SOCl_2$, a hazardous reagent, and the reaction is typically conducted in toxic pyridine.

These factors make the reaction mixture particularly difficult to purify, ultimately leading to low yields, extensive reagent consumption, and significant chemical waste. In contrast, the method described in this work has an AE (%) = 88, employs a green solvent such as acetone, affords high yields, and generally eliminates the need for chromatographic purification.

3. Materials and Methods

3.1. General Information

Unless otherwise specified, all reactions were carried out using dried solvents. The identities of the products were confirmed by comparing them with literature data whenever possible, using ^1H and ^{13}C NMR spectra and HR-MS. The reactions were followed by TLC using silica gel pre-coated aluminum sheets (Macherey Nagel (Düren, Germany): Alugram Xtra SIL GEL UV254 Nr. 818333, thickness 0.2 mm). TLC plates were analyzed under a UV lamp (254 nm). Column chromatography was carried out on silica gel (E. Merck (Darmstadt, Germany), 70–230 mesh). NMR spectra were recorded in $CDCl_3$, $(CD_3)_2SO$, or CD_3OD on a Bruker Avance 400 (Bruker Corp., Billerica, MA, USA) (400 MHz for ^1H, 101 MHz for ^{13}C). For ^1H, ^{13}C chemical shifts are presented in δ-scale as ppm (parts per million) with the residual solvent peak as the reference ($CDCl_3$: 7.26 ppm for ^1H and 77.23 ppm for ^{13}C; $(CD_3)_2SO$: 2.50 ppm for ^1H and 39.51 ppm for ^{13}C; CD_3OD: 3.31 ppm for ^1H and 49.15 ppm for ^{13}C). The description of the multiplicity designations is as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, sept = septet, m = multiplet. MALDI-TOF mass spectrometric analyses were conducted on a Voyager-De Pro MALDI mass-spectrometer (PerSeptive Biosystems, Framingham, MA, USA).

3.2. General Procedure for the Preparation of N-Cinnamoyl-Anthranilic Acids

3.2.1. For Cinnamic Acids Lacking Free Phenolic Groups, Such as 1a, 1c, 1d, and Piperonylic Acid

To a magnetically stirred solution of cinnamic acids (1 mmol) in dry acetone (3 mL), triethylamine (1.1 equivalents, 1.1 mmol, 152 µL) dissolved in dry acetone (2 mL) was added slowly dropwise at room temperature. After a few minutes, the flask containing a clear, light-yellow solution was immersed in an ice bath, and isobutyl chloroformate (1.1 equivalents, 1.1 mmol, 143 µL) dissolved in dry acetone (2 mL) was added dropwise over 15 min. A white precipitate formed, and the mixture was stirred for 20 min at room temperature; at this point, TLC analysis (20% EtOAc in hexane) showed no starting cinnamic acids and a single spot at the front. The mixture was filtered, and the solid was washed with 2 mL of dry acetone.

3.2.2. For Cinnamic Acids with a Single Phenolic Group, Such as 1b and 1e

To a magnetically stirred solution of cinnamic acids (1 mmol) in dry acetone (5 mL), triethylamine (2.2 equivalents, 2.2 mmol, 304 µL) dissolved in dry acetone (5 mL) was added slowly dropwise at room temperature. After a few minutes, the flask containing a clear light-yellow solution was immersed in an ice bath, and isobutyl chloroformate (2.2 equivalents, 2.2 mmol, 286 µL) dissolved in dry acetone (3 mL) was added dropwise over 15 min. A white precipitate formed, and the mixture was stirred for 20 min at room temperature; a TLC control (20% EtOAc in hexane) showed no starting cinnamic acids and

a single spot at the top. The mixture was filtered, and the solid was washed with 2 mL of dry acetone.

3.2.3. For Cinnamic Acids with Two Phenolic Groups, Such as Caffeic Acid, 1f

To a magnetically stirred solution of cinnamic acids (1 mmol) in dry acetone (10 mL), a slow dropwise addition of triethylamine (3.3 eq., 3.3 mmol, 458 µL) dissolved in dry acetone (5 mL) was performed at room temperature. After a few minutes, the flask was placed in an ice bath, and isobutyl chloroformate (3.3 eq., 3.3 mmol, 429 µL) dissolved in dry acetone (5 mL) was added dropwise over 15 min. A white precipitate formed, and the mixture was stirred vigorously for 20 min at room temperature. Afterward, TLC analysis (20% EtOAc in Hexane) indicated no starting material and a single spot in the head. The mixture was filtered, and the solid was washed with 5 mL of dry acetone.

3.2.4. Formation of N-Cinnamoyl-Anthranilic Acids

The acetone solution containing the activated and protected cinnamic acids is added dropwise to the solid aromatic amino acid 2a-d, followed by an additional equivalent of triethylamine (1.05 equivalents). The suspension is then stirred at room temperature for 4 h. During this time, the aromatic amino acid fully dissolves, forming a brown-coloured solution. TLC analysis (70% hexane, 30% EtOAc, 1% AcOH, and 1% MeOH) shows that the protected anhydride has completely disappeared, and a new spot appears with an Rf value lower than that of the initial cinnamic acids. The acetone is completely evaporated using a rotavapor. The residue is then dissolved in 50 mL of ethyl ether, and the mixture is vigorously stirred at room temperature for 1 h. After stirring, the mixture is filtered. The resulting solid is washed twice with petroleum ether (2 × 10 mL) and dried under a stream of N_2. The solid is usually pure by TLC. If small impurities are present, the solid is crystallized with ethyl acetate and hexane. *N*-Cinnamoyl-Anthranilic acids 3a–j were obtained in 72–93% yields.

3.2.5. Formation of 2-Styryl-benzo[*d*][1,3]oxazin-4-ones

To a magnetically stirred solution of *N*-cinnamoyl-anthranilic acids (1 mmol) in dry acetone (5 mL), slowly add triethylamine (1.5 equivalents, 1.5 mmol, 208 µL), dissolved in dry acetone (2 mL), at room temperature. After a few minutes, immerse the flask containing a clear light-yellow solution in an ice bath. Then, add dropwise over 15 min either isobutyl chloroformate (1.5 equivalents, 1.5 mmol, 195 µL) or ethyl chloroformate (1.5 equivalents, 1.5 mmol, 142 µL), both dissolved in dry acetone (3 mL) (for *N*-cinnamoyl-anthranilic acids 3b, 3f, and 3i, three equivalents of TEA/alkyl chloroformate reagent system were used). A white precipitate forms, and the mixture is stirred for 30 min at room temperature. At this point, a TLC check (20% EtOAc in hexane) shows no remaining *N*-cinnamoyl-anthranilic acids and a single spot with a higher R_f. Filter the mixture and wash the solid with 2 mL of acetone. TLC analysis of the filtrate reveals a single spot. Evaporate the filtrate under vacuum, then dissolve the residue in 50 mL of ethyl acetate. Wash this with water (2 × 10 mL), dry over Na_2SO_4, and evaporate under vacuum again.

3.2.6. Carbonate Deprotection and Ring Opening of Benzo[*d*][1,3]oxazin-4-ones Reaction in MeOH

(*E*)-4-(2-(6,7-Dimethoxy-4-oxo-4H-benzo[*d*][1,3]oxazin-2-yl)vinyl)phenyl isobutyl carbonate 4g, (212 mg, 0.5 mmol) is dissolved under an N_2 atmosphere in 5 mL of MeOH (0.1 M). To this solution, 10 equivalents of morpholine (5 mmol, 435 mg, 433 µL) are added dropwise. The dark brown mixture is stirred for 2 h, during which TLC (70% hexane, 30% EtOAc, 1% AcOH, 2% MeOH) confirms the disappearance of the starting material and the appearance of new spots with lower R_f values. The methanolic solution is evaporated in

vacuo. The residue is dissolved in ethyl acetate (50 mL) and treated with a 5% aqueous citric acid solution. The organic phase is separated, washed with water until neutral, dried over Na_2SO_4, and evaporated in vacuo. The crude reaction product shows two spots on TLC analysis and is chromatographed on silica gel (hexane-ethyl acetate, 10–50%).

Reaction in EtOAc

(*E*)-Ethyl (4-oxo-2-styryl-4H-benzo[*d*][1,3]oxazin-6-yl) carbonate 4b, (168 mg, 0.5 mmol), is dissolved under a nitrogen atmosphere in 5 mL of EtOAc (0.1 M). To this solution, 10 equivalents of morpholine (5 mmol, 435 mg, 433 µL) are added dropwise. The dark brown mixture is stirred for 2 h, during which TLC (70% hexane, 30% EtOAc, 1% AcOH, 2% MeOH) confirms the disappearance of the starting material and the appearance of a new single spot with a lower R_f. The reaction mixture is diluted with ethyl acetate (50 mL) and treated with a 5% aqueous citric acid solution. The organic phase is separated, washed with water until neutral, dried over Na_2SO_4, and evaporated in vacuo.

4. Conclusions

The synthetic methodology described here enables the rapid preparation of two valuable classes of 2-aminobenzoic acid derivatives—namely, substituted *N*-hydroxycinnamoyl and *N*-benzoyl-anthranilic acids—as well as the corresponding 4H-benzo[*d*][1,3]oxazin-4-one, through an environmentally sustainable mixed-anhydride process. These procedures require no metal catalysts, do not rely on external heating, and are carried out in green solvents such as acetone, 2-methyltetrahydrofuran, and ethyl acetate, using the alkyl chloroformate/triethylamine system as both an activating and simultaneous protecting reagent. Unlike acyl chlorides, mixed anhydrides function as "soft" acylating agents, and any free phenolic groups present are protected during the activation step rather than during the coupling reaction. This feature results in crude reaction mixtures that can be purified readily by crystallization, affording the desired products in excellent yields. Furthermore, the methodology provides compounds in protected phenolic forms, which offers practical advantages such as enhanced shelf stability and greater versatility for subsequent synthetic elaboration. Compared to traditional procedures described in the literature, the present approach delivers a markedly improved synthetic route that excels in environmental compatibility, operational simplicity, and economic sustainability. Overall, this green, efficient, and broadly applicable strategy provides a viable and scalable platform for the sustainable synthesis of key molecules required for biochemical research and a variety of anticipated applications in organic and medicinal chemistry.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules31040709/s1, Table S1. ^1H, ^{13}C and 2D-NMR data of 3a in $(CD_3)_2SO$; Table S2. ^1H, ^{13}C and 2D-NMR data of 3b in $CDCl_3$; Table S3. ^1H, ^{13}C and 2D-NMR data of 3c in $CDCl_3$; Table S4. ^1H, ^{13}C and 2D-NMR data of 3d in $(CD_3)_2SO$; Table S5. ^1H, ^{13}C and 2D-NMR data of 3e in $(CD_3)_2SO$; Table S6. 1H, 13C and 2D-NMR data of 3f in CD3OD; Table S7. ^1H, ^{13}C and 2D-NMR data of 3g in $CDCl_3$; Table S8. ^1H, ^{13}C and 2D-NMR data of 3h in $CDCl_3$; Table S9. ^1H, ^{13}C and 2D-NMR data of 3i in $(CD_3)_2SO$; Table S10. ^1H, ^{13}C and 2D-NMR data of 3i in $(CD_3)_2SO$; Table S11. ^1H, ^{13}C and 2D-NMR data of 4a in $(CD_3)_2SO$; Table S12. ^1H, ^{13}C and 2D-NMR data of 4b in $CDCl_3$; Table S13. ^1H, ^{13}C and 2D-NMR data of 4c in $CDCl_3$; Table S14. ^1H, ^{13}C and 2D-NMR data of 4d in $CDCl_3$; Table S15. ^1H, ^{13}C and 2D-NMR data of 4e in $(CD_3)_2SO$; Table S16. ^1H, ^{13}C and 2D-NMR data of 4f in $(CD_3)_2SO$; Table S17. ^1H, ^{13}C and 2D-NMR data of 4g in $CDCl_3$; Table S18. ^1H, ^{13}C and 2D-NMR data of 4h in $CDCl_3$; Table S19. ^1H, ^{13}C and 2D-NMR data of 4i in $CDCl_3$; Table S20. ^1H, ^{13}C and 2D-NMR data of 4i in $(CD_3)_2SO$; Table S21. ^1H, ^{13}C and 2D-NMR data of 6g in $(CD_3)_2SO$; Table S22. ^1H, ^{13}C and 2D-NMR data of 5g in $(CD_3)_2SO$; Table S23. ^1H, ^{13}C and 2D-NMR data of 5b in $(CD_3)_2SO$.

Author Contributions: A.Z. and L.L. contributed equally to all aspects of the work, including conceptualization, methodology, software, validation, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, and supervision. All authors have read and agreed to the published version of the manuscript.

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

Abbreviations

The following abbreviations are used in this manuscript:

DMF	Dimethylformamide
HCAs	Hydroxycinnamic acids
iBoc-Cl	Isobutyl chloroformate
Etoc-Cl	Ethyl Chloroformate

References

1. Moussa, Z.; Ramanathan, M.; Al-Masri, H.T.; Ahmed, S.A. Recent progress in the synthesis of benzoxazin-4-ones, applications in N-directed ortho-functionalizations, and biological significance. *Molecules* **2024**, *29*, 5710. [CrossRef]
2. Von Nussbaum, F.; Li, V.M. Neutrophil elastase inhibitors for the treatment of (cardio)pulmonary diseases: Into clinical testing with pre-adaptive pharmacophores. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4370−4381. [CrossRef] [PubMed]
3. Hedstrom, L.; Moorman, A.R.; Dobbs, J.; Abeles, R.H. Suicide inactivation of chymotrypsin by benzoxazinones. *Biochemistry* **1984**, *23*, 1753. [CrossRef] [PubMed]
4. Kopelman, P.; Bryson, A.; Hickling, R.; Rissanen, A.; Rossner, S.; Toubro, S.; Valensi, P. Cetilistat (ATL-962), a novel lipase inhibitor: A 12-week randomized, placebo-controlled study of weight reduction in obese patients. *Int. J. Obes.* **2007**, *31*, 494–499. [CrossRef] [PubMed]
5. Mohareb, R.M.; Mohamed, A.A.; Ibrahim, R.A. Design, synthesis, molecular docking and biological studies of 4*H*-Benzo[*d*][1,3]oxazin-4-one derivatives and their uses in heterocyclic synthesis. *ChemistrySelect* **2022**, *7*, e202200325. [CrossRef]
6. Coppola, G. The chemistry of 4*H*-3,1-benzoxazin-4-ones. *J. Heterocycl. Chem.* **1999**, *36*, 563–588. [CrossRef]
7. Khan, S.A.; Yang, H.; Ying, F.; Chu, C.N.; Lee, T.K.W. Polypharmacology-driven discovery of ZAK-I-57: A potent multi-targeted benzoxazinone small molecule for hepatocellular carcinoma therapy. *MedComm* **2025**, *6*, e70291. [CrossRef]
8. Kumar, P.; Dutta, S.; Batra, D.; Mishra, D.; Kumar, D.; Bhalla, G.; Singh, B.K. Selective functionalization of 2-phenyl-4H-benzo[*d*][1,3]oxazin-4-ones via C–H activation. *Tetrahedron* **2025**, *173*, 134466. [CrossRef]
9. Kumar, P.; Gupta, M.; Bahadur, V.; Parmar, V.S.; Singh, B.K. Radical-induced, palladium-catalyzed C–H activation: An approach to functionalize 4*H*-benzo[*d*][1,3]oxazin-4-one derivatives by using toluenes, aldehydes, and benzyl alcohols. *Eur. J. Org. Chem.* **2018**, *2018*, 1552–1558. [CrossRef]
10. Marasini, B.P.; Rahim, F.; Perveen, S.; Karim, A.; Mohammed Khan, K.; Atta-Ur-Rahman, C.M.I. Synthesis, structure-activity relationships studies of benzoxazinone derivatives as α-chymotrypsin inhibitors. *Bioorg. Chem.* **2017**, *70*, 210–221. [CrossRef]
11. Goel, P.; Jumpertz, T.; Tichá, A.; Ogorek, I.; Mikles, D.C.; Hubalek, M.; Pietrzik, C.U.; Strisovsky, K.; Schmidt, B.; Weggen, S. Discovery and validation of 2-styryl substituted benzoxazin-4-ones as a novel scaffold for rhomboid protease inhibitors. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 1417–1422. [CrossRef]
12. Gataullin, R.R. Advances in the synthesis of aryl-fused six- to nine-membered *N*,*O*-heterocycles. *Russ. Chem. Bull.* **2025**, *74*, 585–622. [CrossRef]
13. Yan, J.; Yang, Z.; Guo, J.; Xue, Q.; Chen, P. Efficient synthesis of 2-aryl-4H-benzo[*d*][1,3]oxazin-4-ones by copper-catalyzed decarboxylation of α-keto acids with anthranilic acids. *Asian J. Org. Chem.* **2024**, *13*, e202400157. [CrossRef]

14. Annor-Gyamfi, J.K.; Bunce, R.A. 4H-Benzo[*d*][1,3]oxazin-4-ones and dihydro analogs from substituted anthranilic acids and ortho-esters. *Molecules* **2019**, *24*, 3555. [CrossRef] [PubMed]
15. Wang, H.-X.; Wei, T.-Q.; Xu, P.; Wang, S.-Y.; Ji, S.-J. I_2/TBHP-mediated oxidative coupling of amino-based bisnucleophiles and isocyanides: Access to 2-aminobenzoxazinones, 2-aminobenzoxazines, and 2-aminoquinazolies under metal-free conditions. *J. Org. Chem.* **2018**, *83*, 13491–13497. [CrossRef]
16. Zheng, Y.; Dong, M.; Qu, E.; Bai, J.; Wu, X.F.; Li, W. Pd-catalyzed carbonylative synthesis of 4*H*-Benzo[*d*][1,3]oxazin-4-ones using benzene-1,3,5-triyl triformate as the CO source. *Chem. Eur. J.* **2021**, *27*, 16219. [CrossRef]
17. Dhawa, U.; Kaplaneries, N.; Ackermann, L. Green strategies for transition metal-catalyzed C–H activation in molecular syntheses. *Org. Chem. Front.* **2021**, *8*, 4886–4913. [CrossRef]
18. Zarrelli, A.; Longobardo, L. Improved chemical synthesis of avenanthramides family and its analogs by mixed anhydride method. *Eur. J. Org. Chem.* **2025**, *28*, e202500169. [CrossRef]
19. Petrillo, F.; Maione, A.; Spampinato, M.; Massa, L.D.; Guida, M.; Zarrelli, A.; Galdiero, E.; Longobardo, L. Antifungal and antibiofilm activities of 2-aminobenzoic acid derivatives against a clinical ocular *Candida albicans* isolate for biomedical applications. *Antibiotics* **2025**, *14*, 432. [CrossRef]
20. Longobardo, L.; Di Fabio, G.; Zarrelli, A. Sustainable chemical derivatization of hydroxycinnamic acids. *ChemistrySelect* **2024**, *9*, e202305046. [CrossRef]
21. DellaGreca, M. Longobardo, L. Protection and Activation of Hydroxycinnamic Acids in Water. *ChemistrySelect* **2020**, *5*, 4588. [CrossRef]
22. Collins, F.W. Oat phenolics: Avenanthramides, novel substituted N-cinnamoylanthranilate alkaloids from oat groats and hulls. *J. Agric. Food Chem.* **1989**, *37*, 60–66. [CrossRef]