Organic & Supramolecular Chemistry

Synthesis of Benzoxazole-2-carboxylate Derivatives: Electronic- and Position-effect of Functional Groups and Computational Modeling of the Selectivity for Oxazole Ring

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In this study, Mitsunobu reagent, DEAD (diethyl azodicarboxylate) and PPh_3, and ethyl-oxalamide derivatives of 2-aminophenol were reacted under mild reaction conditions. As a result of the cyclization reaction, benzoxazole derivatives bearing an ester group in the C-2 position were obtained in a one-pot protocol. It was observed that the electron-donating groups at the C-5 position and the electron-withdrawing groups at the C-6 position of the benzene ring increased the yield of the cyclic product. It was found that the cyclization does not occur when the carboxylic acid group is substituted in the benzene ring. The cyclization reaction we performed preferred the 5-*endo*-*trig* reaction instead of the 6-*exo*-*trig*. This experimental result was examined in detail with density functional theory (DFT) calculations as well. A computational exploration is presented herein that elucidates the detailed mechanism for Huisgen zwitterion's reaction with ethyl-oxalamide derivatives of 2-aminophenol. Potential alternative mechanisms were modeled with DFT calculations *via* CPCM/M06-2X/6-311++G(d,p)//B3LYP/6-31+G(d,p) level method in tetrahydrofuran to understand shed light on the mechanism. Our computational results are in good agreement with experimental findings that benzoxazole derivatives are the sole products in this reaction.

Introduction

The discovery of new synthetic compounds bearing benzoxazole ring and the investigation of their pharmacological activities have become an increasingly prevalent topic. The simultaneous presence of many different benzoxazole derivatives' biological activities is a driving force to find novel procedures to synthesize new drug active substances.[1] The broad pharmacological activities of benzoxazole derivatives, including antibacterial,[2] antifungal,[3] anticancer,[4] anti-inflammatory and antiallergic,[5–6] antimycobacterial,[7] and antihistaminic,[8] antiparkinson,[9] hepatitis C inhibitor,[10] 5-HT3 antagonist,[11] melatonin antagonist,[12] amyloidogenesis inhibitor,[13] and Rho-kinase inhibitor,[14] increase the attractiveness of benzoxazole structures. The central core of the active pharmaceutical ingredients that non-steroidal anti-inflammatory drugs such as Flunoxaprofen and Benoxaprofen, antibiotics Calcimycin, antibacterial drug Boxamycin B and muscle relaxant Chloroxazolone molecules include benzoxazole nucleus (Figure 1).

Among the methods utilized for the formation of benzoxazole rings, the synthesis of a 2-substituted derivative from 2-aminophenol as starting material stands out. Many studies in the literature point out to obtain a high yield benzoxazole ring (Scheme 1A).[15–27] In addition to the necessity in improving the reaction conditions, it is also essential to place the carbonyl group in the C-2 position of the oxazole ring instead of the aryl ring substitution, which will not allow much further derivatizations easily. Lan, Song, and their co-workers synthesized 2-amide-benzoxazole derivatives using S_8-catalyst through triple cleavage of bromodifluoro atoms in bromodifluoro amide derivatives.[28] Although molecular sulfur, a suitable reagent, was used as a catalyst in this reaction, It will not be easy to obtain bromofluoro derivatives. The reaction conditions to obtain these derivatives are also considered as the disadvantage of this study. On the other hand, Hou and co-workers reported the synthesis of 2-acyl-benzoxazole *via* copper-catalyzed direct carboxylation of benzoxazole ring with carbon dioxide.[29] *N*-heterocyclic carbene complex of copper was utilized as the catalyst, and KO*t*Bu was used as a base. Wu et. al reported an approach to the synthesis of 2-acyl-benzoxazole through two steps. The first step was the reaction between 2-aminophenol and lactic acid in 4 M HCl, resulting in benzoxazole ring with ethanol group at the C-2 position. This alcohol group was oxidized using CrO_3, which is not an eco-friendly reagent. They also did not report any substituent on a benzene ring.[30] Dhameliya et al.[31a] reported the reaction of 2-aminophenol (**1**) with ethyl oxalate (**6**) under neutral aqueous conditions without additional reagent. However, they obtained benzoxazin-dione **4** by the cyclo condensation reaction *via* 6-

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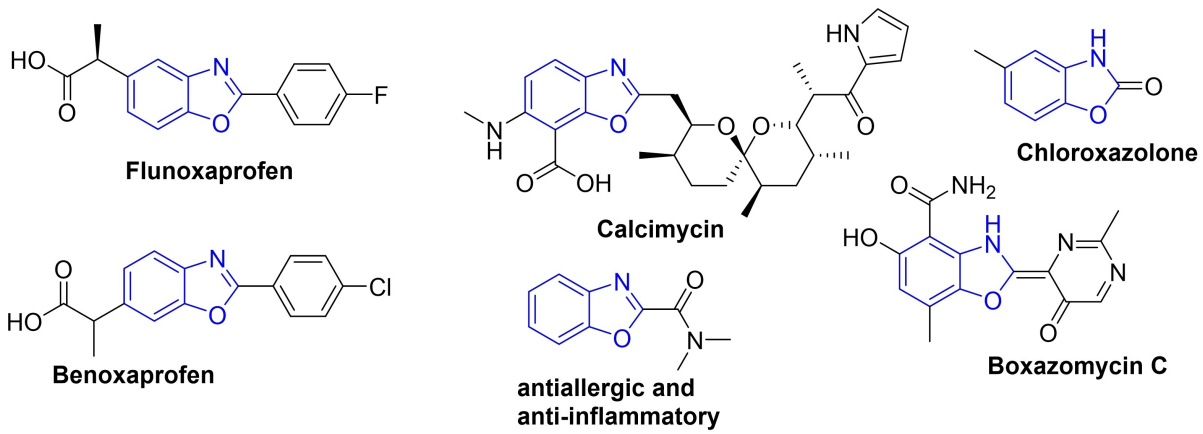
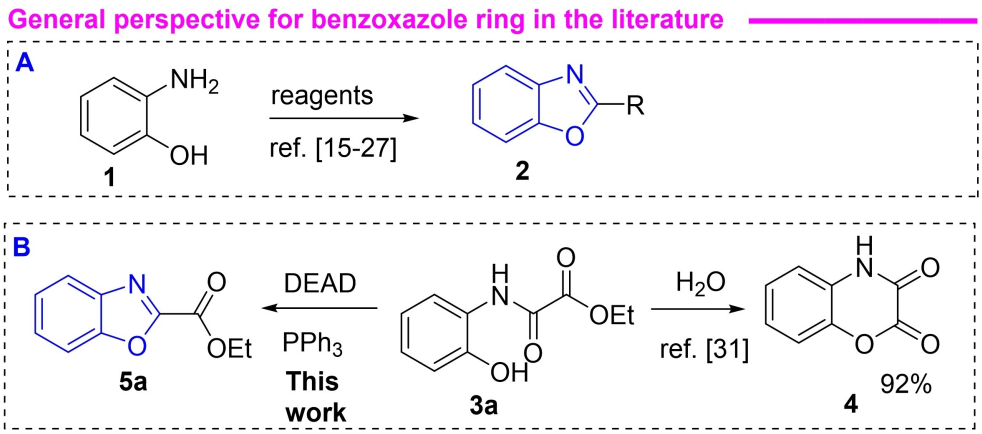


Figure 1. Some biologically active benzoxazole derivatives.



Scheme 1. Two different approaches to the synthesis of benzoxazole derivatives. **A**: general procedure for benzoxazole ring; **B**: One of study in the literature and our approach for synthesis of benzoxazole ring.

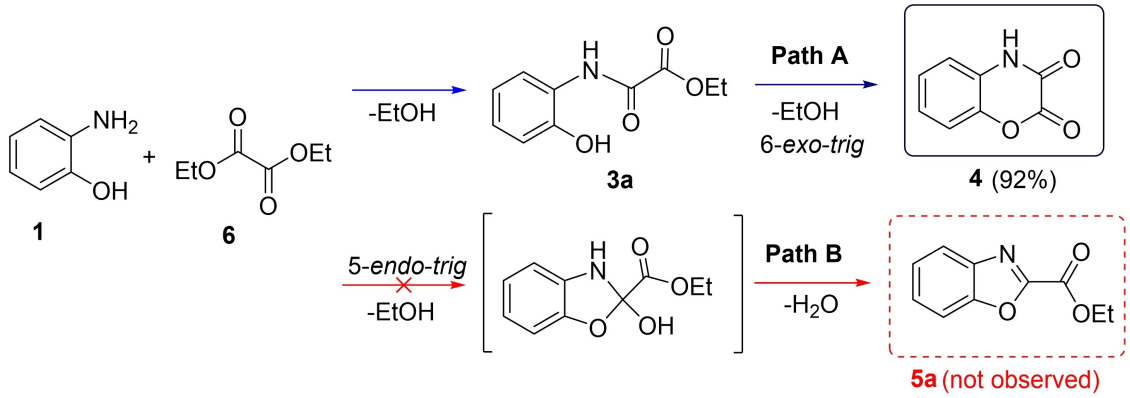
exo-trig instead of benzoxazole derivatives **5** (Scheme 1B). The first Mitsunobu reaction for benzoxazole ring starting from phenol-urea derivative was reported by Liu research group.[31b] Then, Mizojiri et al. reported two different articles that included similar reaction conditions for benzoxazole ring[31c–d] although the studies did not include 2-carbonyl-benzoxazole derivatives. Jacobs et al. have obtained only one 2-carbonyl-benzoxazole derivative by using Mitsunobu reagents in their study.[31e] With the information aforementioned, we want to fulfill the gap by extending the scope of derivatives and discussing the electronic- and position-effect of functional groups on the benzene ring. Moreover, although there is an assumed reaction mechanism for forming the benzoxazole ring, we have investigated the reaction mechanism in detail using the DFT study. The computational study also includes information on the benzoxazole ring's selectivity instead of benzoxazine-dione, which was reported by Dhameliya et al. (Scheme 1B).[31a]

DFT study was reported for the mechanism of the reaction between **1** and **6** in water by Dhameliya et al.[31a] (Scheme 2). Two plausible paths which lead to the formation of and 2H-benzo[b][1,4]oxazine-2,3(4H)-dione **4** (path A) and benzoxazole-2-carboxylate **5a** (path B) through 6-*exo-trig* and 5-*endo-trig* cyclization were proposed, respectively (Scheme 2). They found that path A is kinetically more favorable than path B.[31a]

Dhameliya et al.[31a] described the formation of six-membered ring **4** from the reaction of **1** with **6** in water, we, on the other hand, observed exclusive formation of five-membered benzoxazole ring **5a** from the reaction of **1** and **6** with Huisgen zwitterion obtained from the reaction of DEAD, and PPh_3.[32–34] The apparent difference in the products for the cyclization reactions of **3** prompted us to apply a comprehensive computational investigation of the mechanism.

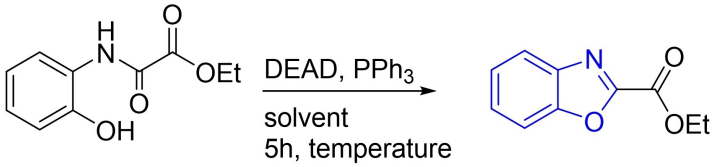
Results and Discussion

To start with the Mitsunobu reagent (DEAD and PPh_3), we have first tested different reaction media to determine the optimum reaction conditions. For this reason, compound **3a** was reacted with DEAD and PPh_3 under different reaction conditions (Table 1). Dry THF was determined to be the most suitable solvent as a result of the reaction conditions tested. It is also observed that the product yield decreases with an increase in



Scheme 2. Proposed mechanism for the formation of **4** and **5a** by Dhameliya et al.

Table 1. Optimization tests for the synthesis of compound **5a**.



Entry	Reaction Conditions Solvent	Additives to reagents	temperature	Yield (**5a**)% [a]
1[b]	1,4-Dioxane	None	0	20
2	1,4-Dioxane	None	25	40
3	1,4-Dioxane	None	60	35
4	1,4-Dioxane	None	80	30
5	Dry THF	None	0	50
6	Dry THF	None	25	49
7	Dry THF	None	60	15
8[c]	Dry THF	N_2 atmosphere	25	50

[a] Isolated yield; [b] although the melting point of 1,4-dioxane is above 0 °C, it does not freeze due to DEAD solution in toluene; [c] it might be due to local relative humidity in our city.

operating temperature (Table 1, entry 7). It has been observed that running the reaction in the open air or an inert atmosphere did not contribute to the product's yield (Table 1, entry 8).

The second part of this study was to uncover the limitation of the approach. For this reason, a variety of substituted 2-aminophenols were utilized (Figure 2). Both mild and strong electron-donating groups, -OMe, -Me, -Cl, and strong electron-withdrawing groups, -NO_2, -CO_2Me, were well tolerated. Yields of final products **5a**–**g** varied between 47–90%. Surprisingly, electron-donating and withdrawing groups at specific positions of the benzene ring affected the yield of products. While unsubstituted benzene derivative **3a** gave benzoxazole derivative **5a** in 50% yield, the -OMe group at the C-5 position of the benzene ring of **3b** resulted in benzoxazole **5b** in 85% yield. Interestingly, the strong electron-withdrawing character of fluorine atom *via* inductive effect at the C-5 position of the benzene ring has almost completely limited the cyclization product (compound **5h**). On the other hand, it has been observed that the carboxylic acid group at the benzene ring (compound **5i**) prevents cyclization completely. The proton transfer from the carboxylic acid group to DEAD or Huisgen zwitterion might explain this issue.

On the other hand, -NO_2 or -CO_2Me groups at the C-6 position (**3d** or **3g**) gave benzoxazole derivatives in 90% (**5d**) and 89% (**5g**) yield, respectively (Figure 2). These results indicate that the electron-donating group at the C-5 position and electron-withdrawing group at the C-6 position increased the cyclization product's yield.

Since electron-donating groups at the C-5 position (para to OH group) strengthen the nucleophilic attack of the phenolic OH group to the amide carbonyl carbon, the yield of the reaction increases (Scheme 3A, structure II) (To see the exact structure of the intermediate, see Scheme 7, compound **20b**). However, the electron-withdrawing groups at the C-6 position (para to the nitrogen atom of amide) reduce the electron density on the amide group's nitrogen atom; thus, the amide group's resonance also weakens. In the resonance form II in Scheme 3B, the lone pair electron on the amide group's nitrogen atom resonates towards the ring with the strong

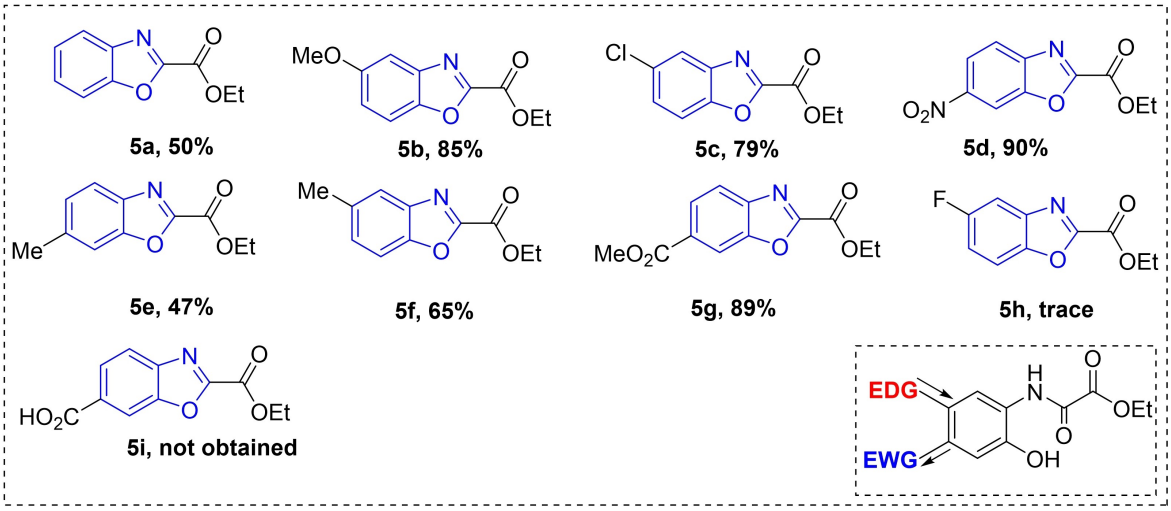
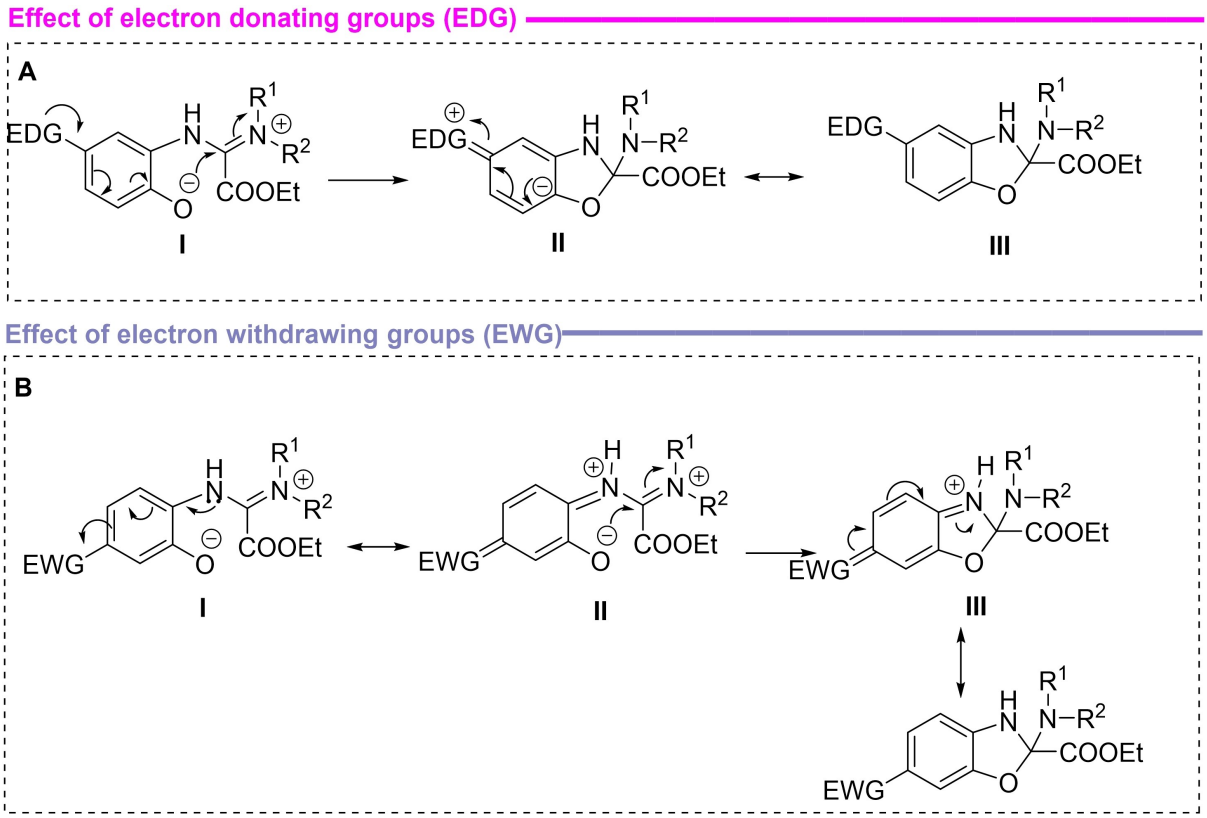


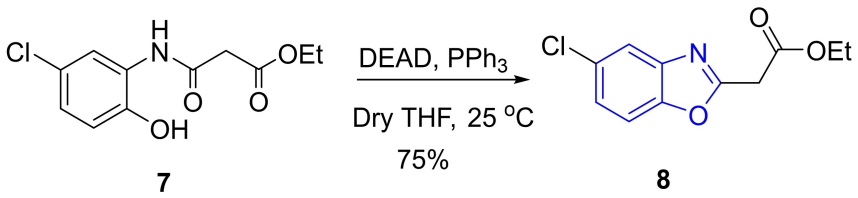
Figure 2. Obtained benzoxazole derivatives.



Scheme 3. Resonance structures of possible reaction intermediate (refers to **20 b** in Scheme 7). **A**: Effect of electron donating groups; **B**: Effect of electron withdrawing groups.

effect of the electron-withdrawing group. This resonance form creates a positive charge on the amide carbon's nitrogen atom, which facilitates the attack of the phenolic OH group to the amide carbonyl carbon and increases the reaction yield.

We have also tested ethyl malonate instead of ethyl oxalate. 2-amino phenol-ethyl malonate **7** under optimum reaction conditions gave a benzoxazole ring with ethyl acetate unit **8** in good yield (Scheme 4).



7 8

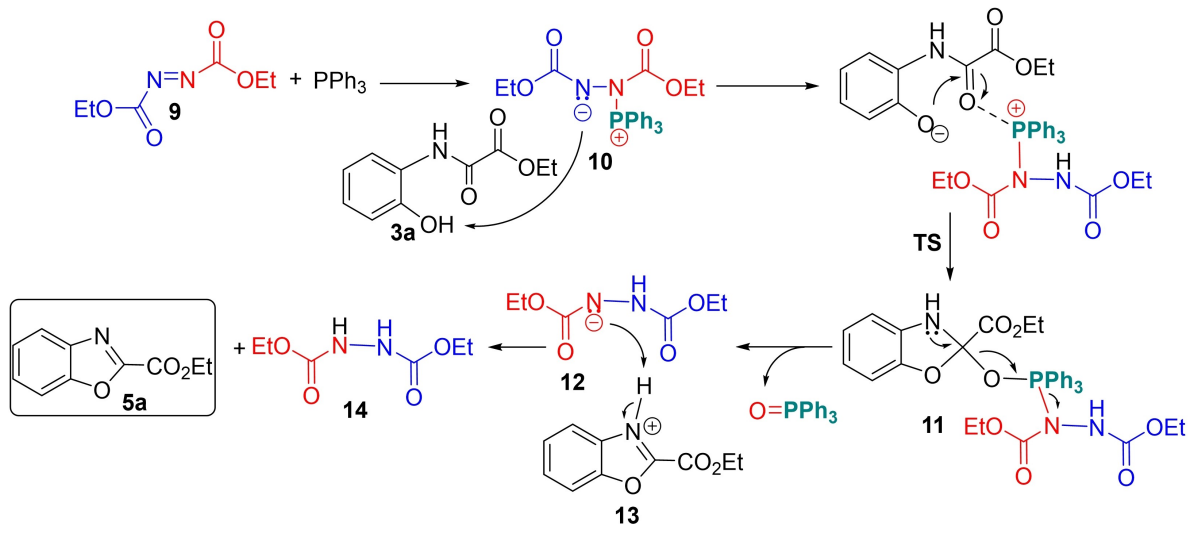
Scheme 4. Synthesis of the benzoxazole-ethylacetate derivative **8**.

Computational Study

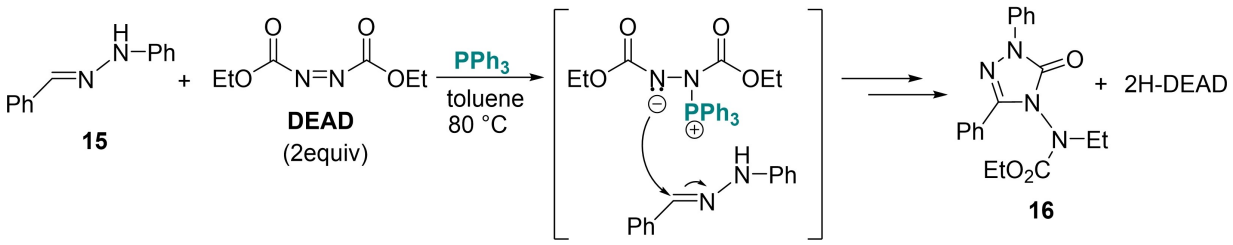
The formation of benzoxazole derivative **5a** from the reaction of Huisgen zwitterion with 2-aminophenol-ethyl glyoxylate **3a** has been theoretically explored to rationalize the experimental observations and to provide insights into the details of the reaction mechanism.

We envisioned that the reaction proceeds through the current and generally accepted mechanism of the Mitsunobu reaction depicted in Scheme 5.[35–36] According to this mechanism, the first step is forming the Huisgen zwitterion **10** by the reaction of DEAD (**9**) with PPh_3. This zwitterion **10** deprotonates the 2-aminophenol-ethyl glyoxylate derivative **3a** and activates the oxygen of the amide carbonyl group. Intramolecular cyclization occurs to form **11**, and subsequently releases $Ph_3P{=}O$, following by a proton abstraction to form the desired product **5a**. Unfortunately, we were unable to locate the transition-state structure **TS** for the attack by negatively charged oxygen.

In 2010, Wang and co-workers[37] reported the synthesis of substituted 4-amino-1,2,4-triazol-3-one **16** by using Huisgen zwitterion with aldehyde hydrazone **15** *via* a cascade reaction (Scheme 6). Their proposed mechanism includes forming a Huisgen zwitterion and the nucleophilic attack of the negatively charged N atom of this ion to the C atom of C=N in aldehyde hydrazone. Computationally, the same reaction step among different reaction channels was also proposed by Zhang et al.[38] This step's energy barrier was found as 20.98 kcal/mol



Scheme 5. Proposed Mitsunobu reaction mechanism for the formation of five-membered benzoxazole ring **5a**.



Scheme 6. The proposed reaction mechanism for the formation of triazol-3-one derivative **16** by Wang and co-workers [37].

using B3LYP/6-311++G(3d,p) method, which is feasible under the experimental conditions.[38]

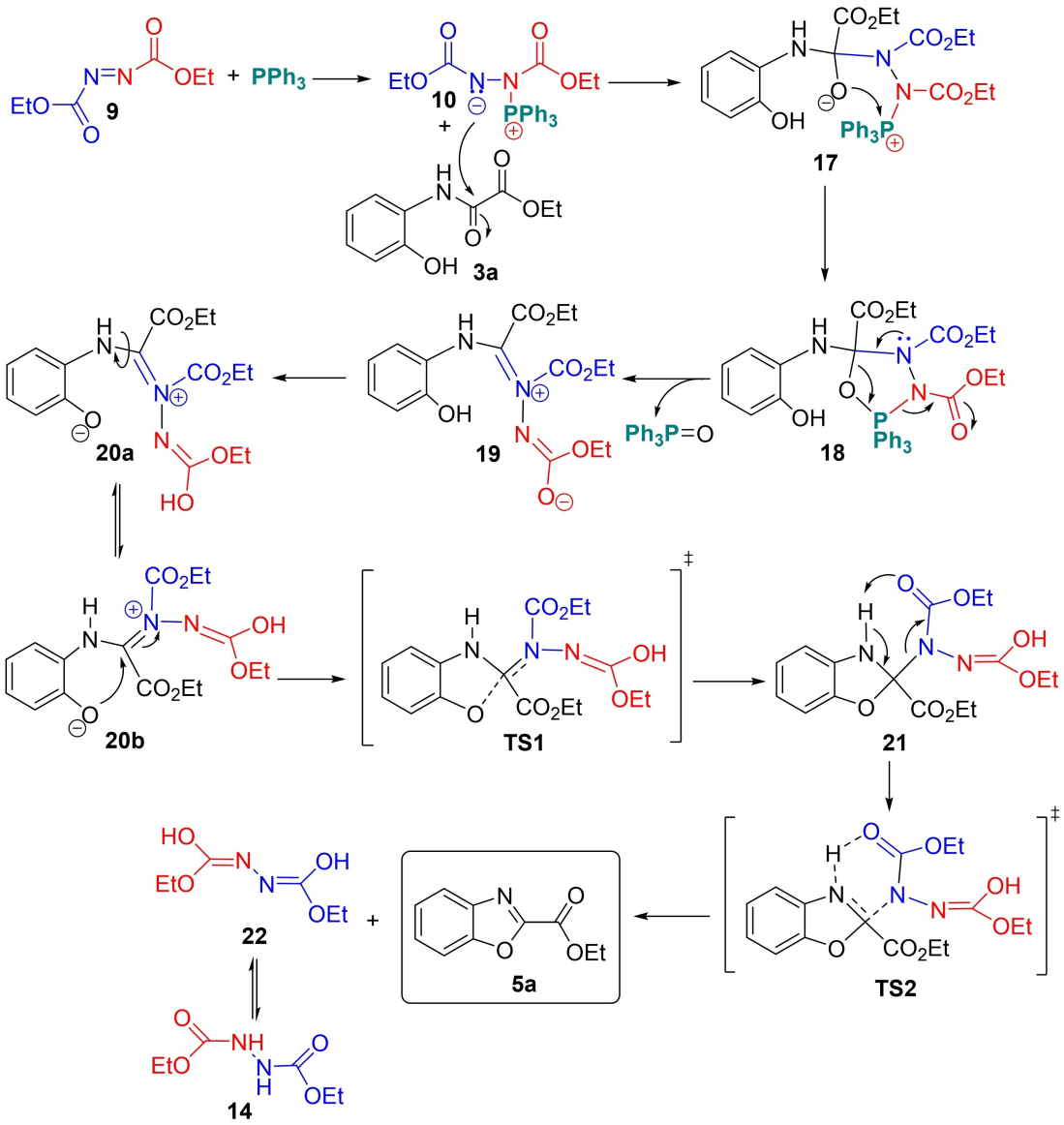
The reaction of Huisgen zwitterions with diaryl-1,2-diones, 1,2-benzoquinones and allenic esters for the synthesis of *N,N*-dicarboethoxy monohydrazones,[39] dihydro-1,2,3-benzoxadiazoles[40] and pyrazolines[41] were reported by Nair et al. All proposed mechanisms for these reactions involve the attack of negatively charged N atom of Huisgen zwitterions on the electrophilic carbon of the substrates.

Based on these studies, we decided to model two alternative mechanisms (mechanism I and II) of Mitsunobu reaction leading to the formation of two different products, benzoxazole derivative **5a** and benzoxazine-dione derivative **4**, respectively, as shown in Scheme 7 and 8.

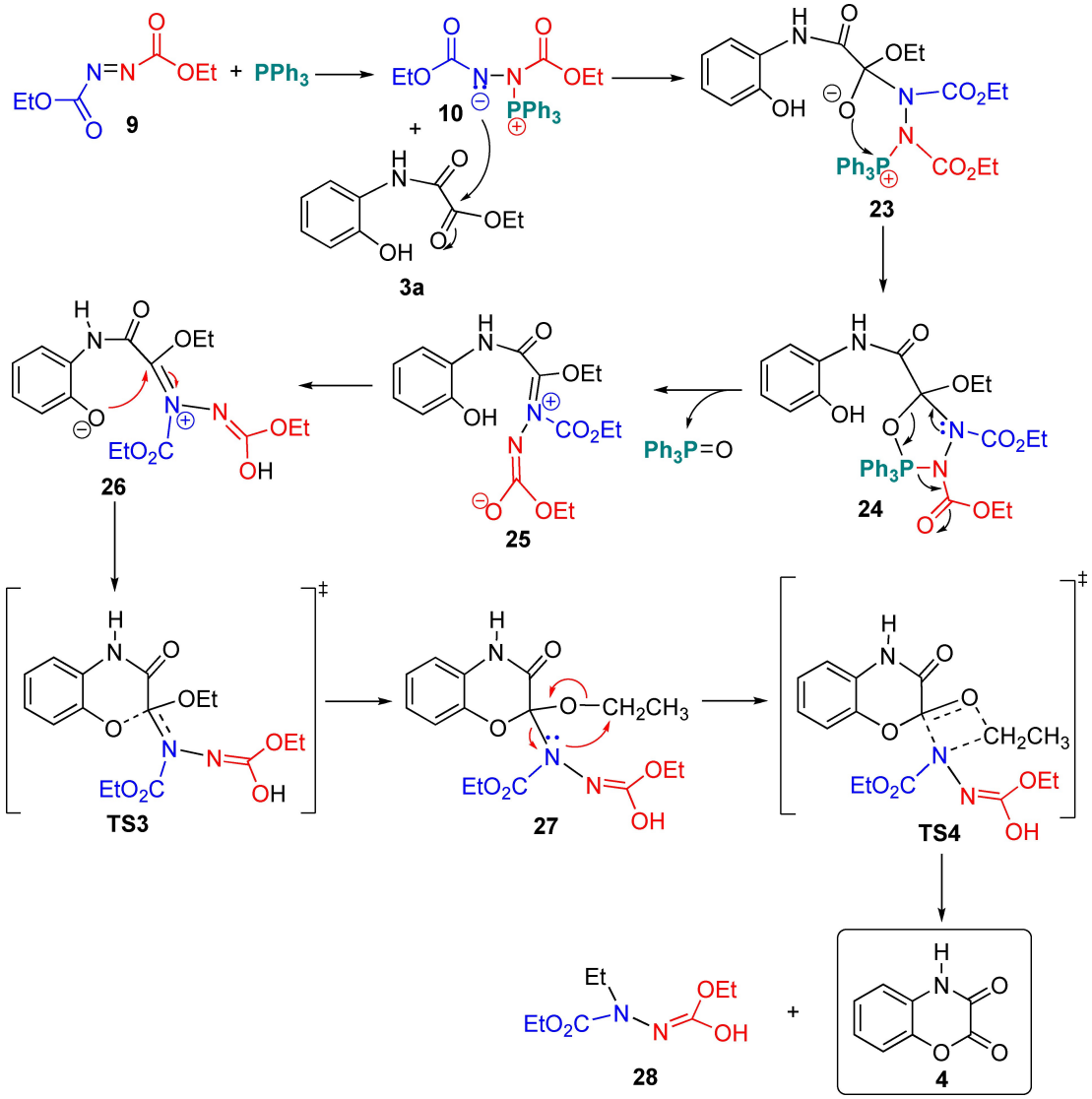
Mechanism I: Formation of benzoxazole 5a

The mechanism leading to **5a** begins with the formation of Huisgen zwitterion **10**. This step of the mechanism was computationally studied in the literature[42a–b] employing DFT calculations and revealed that a Michael-type nucleophilic attack by the phosphine on the azodicarboxylate was preferred over a single electron transfer (SET) process or concerted pericyclic reaction mechanism.

The next step for mechanism I is the nucleophilic attack of negatively charged N of **10** on the amide carbonyl carbon of **3** to form the tetrahedral intermediate **17**, which then undergoes intramolecular cyclization between negatively charged oxygen and positively charged phosphorous atoms to give **18**. Elimination of PPh_3=O accompanied by proton transfer (see compound **19**) results in the formation of **20a**. The following



Scheme 7. Proposed reaction mechanism (mechanism I) for the formation of benzoxazole ring **5a**.



Scheme 8. The reaction mechanism (mechanism II) for the formation of six-membered ring **4**. (For Scheme 8 please use revised form which was upload into the system as revised Scheme 8)

step consists of the rotation of the N–C bond in **20a**, leading to **20b**.

The formation of Huisgen zwitterion **10** and the following steps mentioned above are feasible; therefore, these steps up to the formation of **20b** were not modeled in the present study. The geometries of the structures for the remaining steps from **20b** to **5a** were optimized, and the overall reaction energy profile for mechanism I is given in Figure 3.

- Intramolecular cyclization:

Intramolecular cyclization occurs *via* the nucleophilic attack of oxygen atom O2 on the iminium carbon atom C3. This step proceeds through transition state **TS1** and has a free energy of activation of 4.2 kcal/mol. As shown in Figure 3, the C3-O2 distance diminishes with a corresponding increase in the C1-O2 distance.

- Elimination of 2H-DEAD:

The final step has been found to proceed through a six-membered ring transition state **TS2** (Figure 3), which requires a Gibbs free energy barrier of 5.4 kcal/mol relative to **20b**. The elongation of the bond length of N4-H5 (1.02 Å, 1.10 Å, and 1.87 Å in **21**, **TS2**, and **PC(5a+22)**, respectively) and the shortening of the length of N4-C3 (1.45 Å, 1.34 Å, and 1.30 Å in **21**, **TS2**, **and PC(5a+22)**, respectively) indicate that the N7-C3 bond is broken simultaneously with the nucleophilic attack of the O6 to the H5. The extrusion of the 2H-DEAD affords the desired product **5a**.

Mechanism II: Formation of the six-membered ring (2*H*-1,4-benzoxazine-2,3(4*H*)-dione) 4

Dhameliya et al.[31a] reported the formation of 2*H*-1,4-benzoxazine-2,3(4*H*)-dione (**4**) starting from the same reactants in

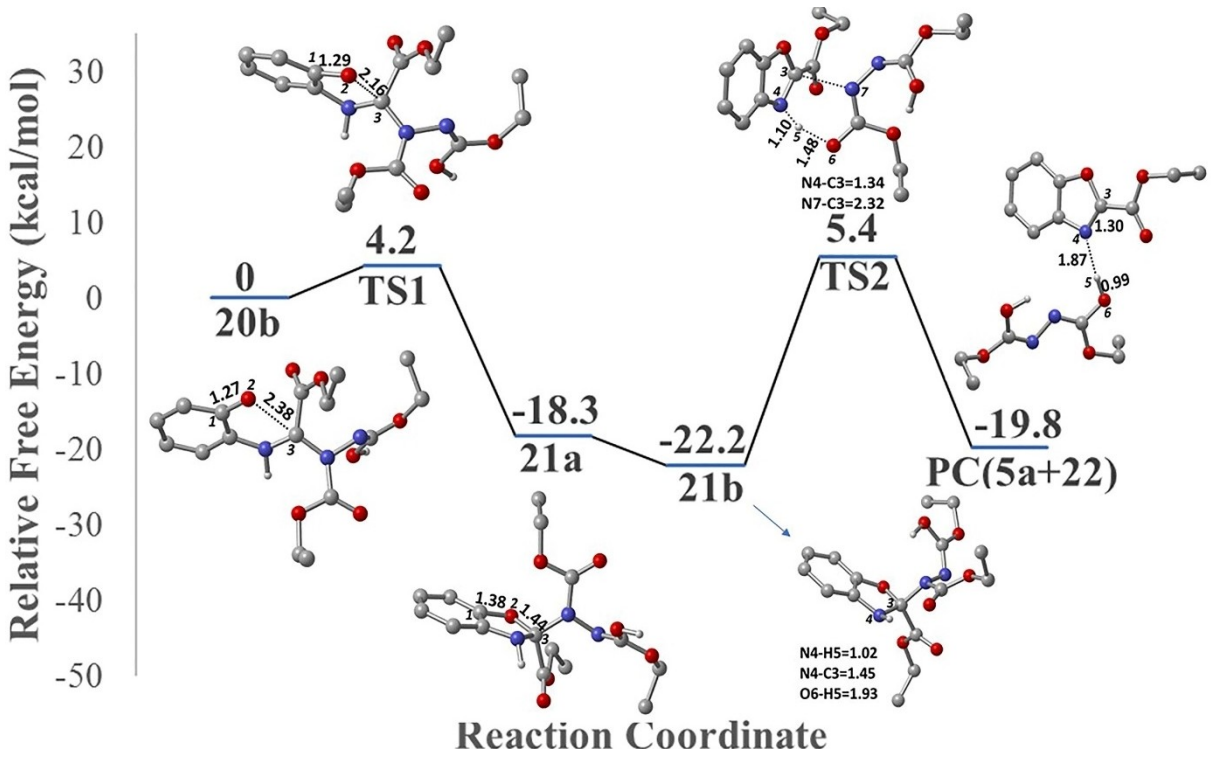


Figure 3. Potential energy profile related to the formation of **5 a** at the CPCM/M06-2X/6-311 + + G(d,p)//B3LYP/6-31 + G(d,p) level in THF. (Polarization effect of the solvent was considered implicitly.) Distances are given in angstroms; angles are in degrees. All C–H hydrogens are omitted for clarity.

different reaction conditions than our case. Therefore, we have modeled this product's formation to provide further inside into the mechanism, even though we do not observe the formation of **4**. After the formation of Huisgen zwitterion **10**, the nucleophilic attack of negatively charged N of **10** on the other carbonyl carbon (ester) of **3 a** can occur. The following processes include (as shown in Scheme 8): (I) formation of five-membered ring **24**; (II) elimination of triphenylphosphine oxide; (III) proton transfer; (IV) intramolecular cyclization; and (V) generation of the product **4**.

Following the same approach with the formation of **5 a**, the geometries of the structures from **26** to **PC**(**4** + **28**) were optimized, and the overall reaction energy profile is given in Figure 4.

Despite numerous attempts, we could not locate **26** and **TS3** on the potential energy surface. Therefore, to obtain an opinion about the energy barrier, the distance between the O2 and C8 has been constrained and all other geometric parameters have been relaxed for the geometry optimization of **26** and **TS3**. The relevant bond lengths of **26** and **TS3** have been constrained to 2.67 and 2.34 Å, respectively. The energy needed to reach the transition state **TS3** from **26** is 7.2 kcal/mol, as shown in Figure 4.

The final step includes the extrusion of **28** *via* four-membered ring transition state **TS4**, which results in the formation of 2*H*-1,4-benzoxazine-2,3(*4H*)-dione **4**. It is the rate-determining step. The calculated free energy of activation for this step has been calculated as 32.3 kcal/mol concerning **26**, and the intrinsic barrier has been found as 66.7 kcal/mol, which is exceptionally high for a reaction occurring at room temperature.

Experimental data collected so far, such as the formation of side product diethyl 1,2-hydrazine dicarboxylate **22 (or 14)**, give some ideas about the reaction mechanism. Formation of **22** is not observed in mechanism II, contrary to the experimental observation, hence clearly revealing that mechanism II is not operative.

Conclusion

An efficient method for the synthesis of previously unknown or hardly accessible 2-carboxylate benzoxazoles has been developed. Eight different benzoxazole derivatives were synthesized in moderate to good yields. Electron donating groups at the C-5 position and electron-withdrawing groups at the C-6 position of the benzene ring were found to increase the cyclization product's yield. The 2-aminophenol derivative with the carboxylic acid group did not yield any cyclization products under the same reaction conditions. It may be due to the abstraction of an acidic proton by the Huisgen zwitterion **10**, the intermediate formed in the reaction conditions, and preventing the progress of the reaction. These observations agree with our theoretical study and support the proposed reaction mechanism (Scheme 7).

The detailed mechanisms for the formation of **4** and **5 a** *via* Huisgen zwitterion formation were investigated using DFT

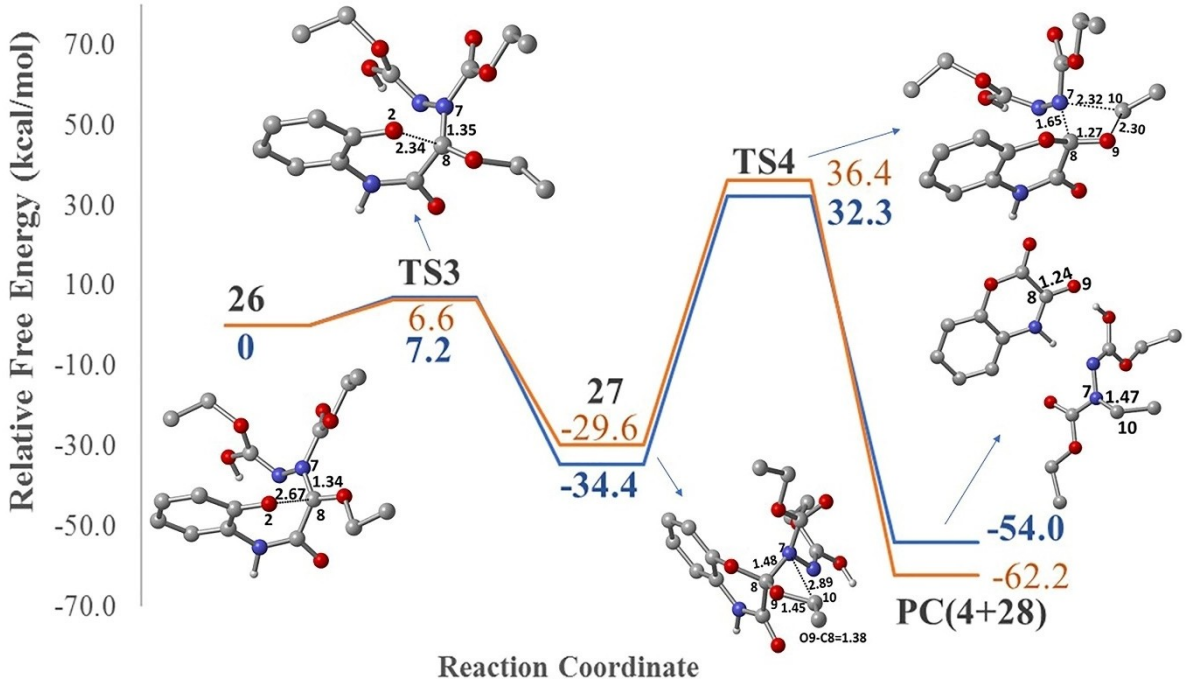


Figure 4. Computed free energy profile related to the formation of **PC**(**4** + **28**) at the CPCM/M06-2X/6-311 + + G(d,p)//B3LYP/6-31 + G(d,p) level in THF (blue). (Polarization effect of the solvent was considered implicitly.) Electronic energies (orange) in the gas phase are reported at the B3LYP/6-31 + G(d,p) level. Distances are given in angstroms; angles are in degrees. All C–H hydrogens are omitted for clarity.

method. We envisioned that two possible competing cyclization mechanisms would give the five- and six-membered-ring products **5a** and **4**, respectively. Formation of the diethyl hydrazine dicarboxylate derivatives **22** and **28** through two-step processes is both exergonic that strongly drives the potential energy profiles downhill. The intrinsic energy barrier of the rate-determining steps of mechanism I was 27.6 kcal/mol, 39.1 kcal/mol less than the one in mechanism II. The proposed mechanistic scenario (Scheme 7) is consistent with the experimentally observed side product: diethyl 1,2-hydrazine dicarboxylate **22**.

We believe that the simplicity of application, rapid synthesis, and the importance of the prepared 2-substituted benzoxazoles make this procedure attractive to synthetic and medicinal chemists. The resulting ester functional group can easily be functionalized for further reaction steps to develop the desired 2-substituted benzoxazole derivatives, convenient in the pharmaceutical industry.

Supporting Information Summary

The general instrumental details, detailed synthetic procedures of performed reactions and analytical characterization of compounds (^{1}H-NMR, ^{13}C-NMR spectra, LC-MS data, and elemental analysis data) data are provided in Supporting Information.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Benzoxazole · 5-exo-trig cyclization · Huisgen zwitterion · Mitsunobu reagent

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