NUCLEOPHILIC RING-OPENING OF BENZOXAZINONES BY DBU: SOME OBSERVATIONS

Sachin B. Baravkar,1 Arup Roy,1 Rupesh L. Gawade,2 Vedavati G. Puranik,2 and Gangadhar J. Sanjayan1
1Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune, India
2Center for Materials Characterization, CSIR-National Chemical Laboratory, Pune, India

GRAPHICAL ABSTRACT

Abstract This communication demonstrates the formation of an unusual nucleophilic ring opening of benzoxazinones by 1,8-diazabicycloundec-7-ene (DBU). This observation contradicts the intrinsic feature of a hindered nonnucleophilic base like DBU. Confirmation of the product was achieved via single-crystal X-ray diffraction studies.

Keywords Benzoxazinones; caprolactam; DBU; HATU

INTRODUCTION

1,8-Diazabicycloundec-7-ene (DBU) is a well-known bicyclic amidine-based nonnucleophilic strong base used in numerous reactions.[1] Its use as a dehydrohalogenation reagent has been of great importance.[2] However, there are instances wherein DBU has been observed to act as a nucleophile.[3] For example, DBU undergoes 1,4-addition with diarylpyrone when heated at 120 °C.[4] Also, it reacts with pyrazoles to generate an unusual DBU adduct.[5]

Our group has been involved in developing aromatic–aliphatic hybrid oligomers, where anthranilic acid (Ant) is used as a building block. Ant unit, when coupled with a constrained amino acid like proline (Pro) at the C-terminus,
generated a nine-membered hydrogen-bonded network formed in the forward direction of the sequence (1 → 2 amino acid interactions).\[6\] Using (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (i.e., HATU) as a coupling agent, segment doubling strategy of the monomer units proceeded readily to afford oligomers that exhibited helical conformation.\[7\] However, the trimer unit AcNH-Ant-Ant-Pro-NHMe, having an additional Ant unit at the N-terminus, displayed the presence of C\(_{11}\) and C\(_{10}\) H-bonded networks in the folded unit.\[8\] Further investigations about the role of each H-bonded network revealed that the stability of the entire folded architecture necessitates the participation of each interaction in a cooperative manner. To get more insight into the hydrogen-bonding propensities in a foldamer sequence, we aimed to investigate the effect of introduction of a flexible amino acid like glycine (Gly) at the C-terminus of the trimer segment AcNH-Ant-Ant-Pro-NHMe. The coupling of the Ant-Ant unit with Pro has been observed to proceed via the formation of benzoxazinone as an intermediate instead of the coupled product as shown in Fig. 1. This is because of the intramolecular cyclization caused by activation of carboxylic acid unit.

Benzoxazinones, owing to their interesting biological properties, form a very important class of compounds\[9\] and have been found to act as major defensive secondary metabolites in wheat, rye, and maize, among others.\[10\] Some of the derivatives of benzoxazinone are also known to display intriguing antiphlogistic properties.\[9\] Anthalexine, a close derivative of benzoxazinone, finds application as an antibacterial agent.\[11\] Furthermore, substituted benzoxazinones are known as promising inhibitors of serine proteases of the chymotrypsin superfamily.\[12\]

Benzoxazinones are relatively stable and can easily be isolated and characterized, often owing to the presence of extended conjugation in them.\[13\] Once they are formed during the course of the reaction, they interfere with the coupling reaction.\[14\] To obtain the corresponding peptide sequence, benzoxazinone has to be further reacted with the desired amine in the presence of a base. We have earlier attempted to react benzoxazinones with amines, aided by a range of catalysts with varying success.\[8,15\] The reaction proceeds by nucleophilic amino group attacking the carbonyl carbon of benzoxazinone, and subsequent ring opening gives the desired coupled product. It has also been observed that the reaction rate increases with the number of electron-withdrawing substituents on the aromatic rings of the benzoxazinone. Similarly, the increase in the electron density at the nucleophilic amino group enhances the reaction rate. Errede et al. has briefly explained the factors affecting the rate of the reaction between the benzoxazinone (acylanthranils) and an amine.\[16\]

**Figure 1.** Formation of coupled product, along with benzoxazinone.
RESULTS AND DISCUSSION

Our strategy here was to construct the tetramer sequence NO₂-Ant-Ant-L-Pro-Gly-NH₂ via the formation of corresponding benzoazinone, which can further be reacted with dimer amine L-Pro-Gly-OMe to obtain the desired tetramer as shown in Scheme 1. Thus, the synthesis started with the generation of acid chloride counterpart of benzoic acid analog 1, which was reacted with methyl-2-chloro-5-aminobenzoate 2 to get the dimer 3 in 61% yield. Similarly, dimer 7 was obtained in very good yield when the amine 5 was treated with benzoyl chloride 6. The methyl ester of dimer 3 was then subjected to basic hydrolysis, followed by converting it to benzoazinone 4 by using EDC·HCl as a coupling agent in a 79% yield over two steps. Likewise, oxazinone 8 was prepared. The dimer 11a was obtained on coupling Boc-L-Proline with Gly-OMe using EDC·HCl as a coupling agent followed by treatment with methanolic methylamine. This was subjected to Boc deprotection followed by reaction with benzoazinones 4 and 8, respectively, in the presence of DBU as a base to get the desired tetramers 12a and 12b in good yields.

Scheme 1. Synthesis of benzoazinones, amine, and their reaction in the presence of DBU.
However, along with tetramers 12a and 12b, we also came across the formation of side products 13a and 13b.\textsuperscript{[19]} To get a clear idea about the structure of the side product, we undertook extensive efforts to crystallize the said compounds. This resulted in the formation of single crystals of 13a (Fig. 2). Solid-state conformational analysis finally helped us to unravel the structure of the side product 13a. It became apparent that a DBU molecule got coupled with the dimer sequence NO2-Ant-Ant-OH, which in turn opens up to form a caprolactam. The single-crystal structure also suggested the presence of an intraresidual six-membered hydrogen bonding (C\textsubscript{6}).

The plausible mechanism for the formation of products 13a and 13b is depicted in Scheme 2. First, the lone pair on imine nitrogen atom of DBU attacks the more electrophilic carbonyl carbon of benzoxazinone, resulting in its opening with the formation of the zwitterionic intermediate, which picks up water during workup, leading eventually to the formation of the aminopropyl caprolactam.

**EXPERIMENTAL**

All the chemicals and reagents were obtained commercially. Column chromatographic purifications were done with 230- to 400-mesh silica gel. NMR spectra were recorded in CDCl\textsubscript{3} on AV 400-MHz Bruker NMR spectrometers. All chemical shifts are reported in parts per million (ppm) downfield to tetramethylsilane (TMS) and peak multiplicities are referred to as singlet (s), doublet (d), quartet (q), and
multiplet (m). Melting points were determined on a Buchi melting-point B-540 instrument.

**General Procedure for the Preparation of 12a, 12b, 13a, and 13b**

Benzoxazinone 4/8 (1 equiv) was taken in a two-necked, round-bottomed flask. Next, the amine 11b (1.2 equiv) obtained by the Boc-deprotection\(^{[18]}\) of 11a by exposing it to trifluoroacetic acid–dichloromethane (TFA-DCM) (1:1) for 1 h was dissolved in DMF (2 mL) and added to the round-bottomed flask containing 4/8, followed by the dropwise addition of DBU (1.5 equiv) at 0°C. The reaction mixture was kept at room temperature for 3 h. After completion of the reaction, DCM was added to the reaction mixture and the combined organic layer was washed with saturated KHSO\(_4\) solution and saturated brine solution repeatedly to ensure complete removal of DMF. The DCM layer was dried over anhydrous Na\(_2\)SO\(_4\) and the solvent was concentrated under reduced pressure to get the crude product. The crude product was further purified by using column chromatography to separate the products 12a/12b and 13a/13b.

**CONCLUSIONS**

In summary, we have reported the formation of an unusual product discovered during the coupling reaction of benzoxazinone and amino acid, mediated by DBU. Structures of the compounds were confirmed by \(^1\)H and \(^1\)C NMR spectroscopy and single-crystal X-ray diffraction studies.\(^{[20]}\) This finding assumes importance, because it contradicts the general belief that DBU is a nonreactive hindered organic base, frequently used in diverse organic transformations.

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**SUPPLEMENTARY INFORMATION**

Full experimental details for compounds 3, 4, 12a, 12b, 13a, and 13b including mass, \(^1\)H and \(^1\)C NMR spectra, and crystal data, can be accessed on the publisher’s website.

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