A Zinc-Mediated Deprotective Annulation Approach to New Polycyclic Heterocycles

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Abstract: A straightforward approach to new polycyclic heterocycles, 1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-ones, is presented. It is based on the ZnCl2-promoted deprotective 6-endodig heterocyclization of N-Boc-2-alkynylbenzimidazoles under mild conditions (CH2Cl2, 40 °C for 3 h). The zinc center plays a dual role, as it promotes Boc deprotection (with formation of the tert-butyl carbocation, which can be trapped by substrates bearing a nucleophilic group) and activates the triple bond toward intramolecular nucleophilic attack by the carbamate group. The structure of representative products has been confirmed by X-ray diffraction analysis.

Keywords: alkynes; annulation; benzimidazoxazinones; heterocycles; polycyclic heterocycles; heterocyclization; zinc

1. Introduction

The development of efficient methods for the synthesis of high value added polycyclic heterocyclic derivatives by metal-promoted annulation of acyclic precursors is one of the most important areas of research in heterocyclic chemistry [1–5]. Polycyclic heterocyclic systems, in fact, are largely present as fundamental cores in natural products and in biologically active compounds [6–11], and the possibility to obtain them by a simple cyclization process starting from readily available substrates is particularly attractive [1–5].

Among acyclic substrates able to undergo a metal-promoted cyclization to give a polycyclic heterocycle, functionalized alkynes bearing a suitably placed heteronucleophile play a major role, as the triple bond can be easily electrophilically activated by a suitable metal species thus promoting the cyclization by intramolecular nucleophilic attack [1–5]. Usually, processes like these are promoted by costly metals (mainly gold [12–19], palladium [20–23], rhodium [24–26], platinum [27–29], and, occasionally, ruthenium [30]), while the use of less expensive metal species, such as cobalt [31], nickel [32], copper [33–36], zinc [37–40], and silver [41,42] compounds, has been scantily reported in the literature, and applied to a limited number of examples.

In this work, we report on the use of very simple and inexpensive ZnCl2 as a promoter for the efficient deprotective heterocyclization of N-Boc-2-alkynylbenzimidazoles 1, to give access to novel polycyclic heterocycles, that are, 1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-ones 2 (Scheme 1). It is worth mentioning in this context that the cyclization of O-Boc propargyl alcohols to give 4H-1,3-dioxin-2-ones and/or 4-alkylidene-1,3-dioxolan-2-ones
has been previously reported to occur with mercuric triflate as the catalyst [43]. It is also important to note that some excellent reviews on Zn-catalyzed reactions have appeared in the recent literature [44–48].

![Scheme 1](image)

**Scheme 1.** This work: ZnCl₂-assisted heterocyclization of N-Boc-alkynylbenzimidazoles 1 to benzimidazoxazinones 2.

### 2. Results and Discussion

It is well known that zinc (II) compounds are able to promote Boc deprotection [49–54]. In particular, an excess of ZnBr₂ has been successfully employed for the deprotection of N-Boc secondary amines [52] as well as of tert-butyl esters [53,54]. Considering the importance of developing new approaches to the synthesis of polycyclic heterocycles by heterocyclization processes promoted by non-noble and inexpensive metal species, we have explored the possibility to access new polycyclic heterocycles, that are 1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-ones 2, starting from readily available N-Boc-2-alkynylbenzimidazoles 1, by Zn(II)-assisted deprotective heterocyclization (Scheme 1). According to our rationale, the zinc center should play a double role, that is, to promote deprotection to give a carbamate species A (with elimination of isobutene and H⁺ from the ensuing tert-butyl carbocation [52–54]) and then assist a 6-endo-dig heterocyclization by intramolecular nucleophilic attack of the free carbamate group of species B (in equilibrium with A) on the triple bond activated by coordination to Zn²⁺ (with the zinc center stabilized by chelation by the benzimidazole nitrogen). This would lead to organozinc intermediate C, whose protonolysis would then afford the polycyclic heterocycles 2 (Scheme 2; zinc counteranions have been omitted for clarity).

![Scheme 2](image)

**Scheme 2.** Mechanistic hypothesis for the formation of polycyclic heterocycles 2 by Zn²⁺-mediated sequential deprotection - 6-endo-dig heterocyclization of N-Boc-alkynylbenzimidazoles 1.

The first experiments were performed using N-Boc-2-(hex-1-in-1-yl)-1H-benzo[d]imidazole 1a as substrate (R¹ = H, R² = Bu) (prepared by alkylation of N-Boc-2-bromo-1H-benzo[d]imidazole, see the Supplementary Materials for details), which was allowed to react in CH₂Cl₂ as the solvent at room temperature in the presence of ZnBr₂ (1 equiv). Under these conditions, after 3 h reaction time, substrate conversion was 51%, while the desired 3-buty-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2a was isolated in 25% yield. The structure of 2a was unequivocally confirmed by XRD analysis (see the
Supplementary Materials for XRD data). The X-ray structure of 2a, shown in Figure 1, confirmed that the heterocyclization process at intermediate B level occurred in a 6-endo-dig fashion (with closure to a 6-membered ring) rather than in the possible alternative 5-exo-dig fashion (with closure to a five-membered ring).

Figure 1. Molecular structure of 3-butyl-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2a. Color legend: carbon (light grey), hydrogen (white), oxygen (red), nitrogen (blue) (CCDC 2050576).

In spite of the low yield, this initial result was encouraging, since it confirmed the validity of our work hypothesis and the possibility to synthesize novel polycyclic heterocycles with a very simple approach and using an inexpensive promoter. In order to improve the reaction performance, and achieve a higher 2a yield, we then changed some operative parameters (Table 1, entries 2–9). Practically no reaction occurred by changing the solvent to MeOH (Table 1, entry 2), while only traces of 2a were detected in acetone (Table 1, entry 3). Lowering the amount of ZnBr₂ significantly suppressed the reaction (Table 1, entry 4). On the other hand, the use of 1.5 or 2 equiv of ZnBr₂ was beneficial, 2a being formed in ca. 70% isolated yield (Table 1, entries 5 and 6, respectively). Better results with respect to the parent reaction (Table 1, entry 1) were also obtained by increasing the 1a concentration from 0.5 (Table 1, entry 1) to 1 mmol/mL of CH₂Cl₂ (Table 1, entry 7), while more diluted conditions led to a lower 2a yield (Table 1, entry 8). Predictably, a faster reaction was observed at 40 °C rather than 25 °C, with a higher yield of 2a (Table 1, entry 9) with respect to the initial experiment (Table 1, entry 1). Under the optimized conditions (40 °C in CH₂Cl₂ in the presence of 1.5 equiv of ZnBr₂, with a substrate concentration of 1 mmol per mL of solvent), 2a could be finally obtained in a yield as high as 79% (Table 1, entry 10).

Very interestingly, the reaction was also successful using ZnCl₂ (Table 1, entry 11) or ZnL₂ (Table 1, entry 12), the best results in terms of 2a yield being obtained with ZnCl₂ (82%, Table 1, entry 11). This result, associated with the lower cost of ZnCl₂, made ZnCl₂ the promoter of choice for realizing the transformation of 1a into benzimidazoxazinone 2a and for the subsequent extension to other differently substituted substrates (Table 2).

Thus, to assess the generality of the reaction, various N-Boc-alkynylbenzimidazoles 1 (bearing different R¹ and R² groups; prepared as detailed in the Supplementary Materials) were subjected to the optimized reaction conditions with ZnCl₂ as the promoter (Table 2, entries 2–15).
Table 1. ZnX₂-promoted deprotective heterocyclization of N-Boc-2-(hex-1-in-1-yl)-1H-benzo[d]imidazole 1a under different conditions.

![Chemical structure of 1a](image)

| Entry | ZnX₂ (Equiv) | T (°C) | Solvent   | Concentration of 1a | Conversion of 1a (%) | Yield of 2a (%) |
|-------|--------------|--------|-----------|---------------------|----------------------|-----------------|
| 1     | ZnBr₂ (1)    | 25     | CH₂Cl₂    | 0.5                 | 51                   | 25              |
| 2     | ZnBr₂ (1)    | 25     | MeOH      | 0.5                 | 3                    | 0               |
| 3     | ZnBr₂ (1)    | 25     | acetone   | 0.5                 | 12                   | Traces          |
| 4     | ZnBr₂ (0.5)  | 25     | CH₂Cl₂    | 0.5                 | 9                    | 6               |
| 5     | ZnBr₂ (1.5)  | 25     | CH₂Cl₂    | 0.5                 | 100                  | 72              |
| 6     | ZnBr₂ (2)    | 25     | CH₂Cl₂    | 1.0                 | 62                   | 70              |
| 7     | ZnBr₂ (1)    | 25     | CH₂Cl₂    | 0.2                 | 42                   | 10              |
| 8     | ZnBr₂ (1)    | 40     | CH₂Cl₂    | 0.5                 | 100                  | 63              |
| 9     | ZnBr₂ (1)    | 40     | CH₂Cl₂    | 1.0                 | 100                  | 79              |
| 10    | ZnCl₂ (1.5)  | 40     | CH₂Cl₂    | 1.0                 | 100                  | 82              |
| 11    | ZnCl₂ (1.5)  | 40     | CH₂Cl₂    | 1.0                 | 100                  | 77              |

*All reactions were carried out for 3 h. *Mmol of starting 1a per mL of solvent. *Based on unreacted 1a, upon isolation from the reaction mixture. *Isolated yield based on starting 1a.

Table 2. Synthesis of 1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-ones 2 by ZnCl₂-promoted deprotective heterocyclization of N-Boc-2-alkynylbenzimidazoles 1.

![Chemical structure of 2](image)

| Entry | 1 | 2 | Yield of 2 (%) |
|-------|---|---|----------------|
| 1     | ![1a](image) | ![2a](image) | 82 |
| 2     | ![1b](image) | ![2b](image) | 77 |
| 3     | ![1c](image) | ![2c](image) | 76 |
| 4     | ![1d](image) | ![2d](image) | 83 |
Table 2. Cont.

| Entry | 1          | 2          | Yield of 2 (%)<sup>b</sup> |
|-------|------------|------------|-----------------------------|
| 5     | ![Chemical Structure](image1) | ![Chemical Structure](image2) | 77                          |
| 6     | ![Chemical Structure](image3) | ![Chemical Structure](image4) | 45<sup>c</sup>              |
| 7     | ![Chemical Structure](image5) | ![Chemical Structure](image6) | 30<sup>d</sup>              |
| 8     | ![Chemical Structure](image7) | ![Chemical Structure](image8) | 85                          |
| 9     | ![Chemical Structure](image9) | ![Chemical Structure](image10) | 82                          |
| 10    | ![Chemical Structure](image11) | ![Chemical Structure](image12) | 80                          |
| 11    | ![Chemical Structure](image13) | ![Chemical Structure](image14) | 70                          |
| 12    | ![Chemical Structure](image15) | ![Chemical Structure](image16) | 66                          |
| 13    | ![Chemical Structure](image17) | ![Chemical Structure](image18) | 60                          |
| 14    | ![Chemical Structure](image19) | ![Chemical Structure](image20) | 74                          |
As can be seen from Table 2, entries 2–5, excellent results were obtained with substrates still with $R^2 = \text{Bu}$ and bearing either electron-donating (methyl or methoxy; yields of the corresponding products 2b–d were 76–83%, Table 2, entries 2–4) or electron-withdrawing chlorine substituents (yield of 2e = 77%, Table 2, entry 5) on the aromatic ring. On the other hand, inferior results were observed with substrates 1f and 1g, bearing a strong electron-withdrawing nitro substituent (yields of 2f and 2g were 45% and 30%, Table 2, entries 6 and 7, respectively). With these substrates, complete Boc removal competed with heterocyclization, as confirmed by the formation of not negligible amounts of deprotected compounds 3f and 3g (20% and 31%, respectively, Table 2, entries 6 and 7) (Scheme 3), not observed in other cases. Clearly, the formation of these byproducts from substrates 1f and 1g is due to the diminished nucleophilicity of the carbamate intermediate B (Scheme 2) caused by the strong electron-withdrawing effect of the nitro group, which makes decarboxylation to compete with cyclization. The structures of products 2c and 2f were confirmed by XRD analysis (see the Supplementary Materials for XRD data). The X-ray structures of 2c and 2f, shown in Figures 2 and 3, respectively, allowed to unequivocally establish the positions of the methoxy and nitro substituents in regiosomeric substrates 1c/1d and 1f/1g, respectively (as 2c must be formed from 1c and 2f from 1f).

![Scheme 3. Formation of byproducts 3f and 3g (Table 2, entries 6 and 7) by Boc deprotection of nitro-substituted substrates 1f and 1g, competitive with heterocyclization.](image)

![Figure 2. Molecular structure of 3-butyl-8-methoxy-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2c. Color legend: carbon (light grey), hydrogen (white), oxygen (red), nitrogen (blue) (CCDC 2051334).](image)
As can be seen from Table 2, entries 2–5, excellent results were obtained with substrates bearing a methoxymethyl (yield of 2m, 60%; Table 2, entry 13) or a 2-(methoxycarbonyl) ethyl (yield of 2n, 74%; Table 2, entry 14) group. Interestingly in the case of N-Boc-4-(1H-benzo[d]imidazol-2-yl) but-3-yn-1-ol 1o, bearing a 2-hydroxyethyl group on the triple bond, the tert-butyl group was incorporated into the final product to give 3-(2-((tert-butoxy)ethyl)-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2o′ (66% yield; Table 1, entry 15). This is clearly due to the trapping of the tert-butyl carbocation, ensuing from deprotection, by the nucleophilic hydroxyl group, as shown in Scheme 4.

![Figure 3. Molecular structure of 3-butyl-8-nitro-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2f. Color legend: carbon (light grey), hydrogen (white), oxygen (red), nitrogen (blue) (CCDC 2050711).](image-url)

**Scheme 4.** Plausible mechanism for the formation of product 2o′ (chloride anions are omitted for clarity).

### 3. Materials and Methods

#### 3.1. General Experimental Methods

Melting points were measured with a Leitz Laborlux 12 POL polarizing optical microscope (Leitz Italia GmbH/Srl, Lana(BZ), Italy) and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded at 25 °C in CDCl$_3$ or DMSO-d$_6$ at 300 MHz or 500 MHz and 75 or 125 MHz, respectively, with Me$_4$Si as internal standard, using Bruker DPX Avance 300 and Bruker DPX Avance 500 NMR spectrometers (Bruker Italia s.r.l., Milano, Italy); chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with a JASCO FT-IR 4200 spectrometer (Jasco Europe s.r.l., Cremella, Lecco, Italy). All reactions were analyzed by TLC on silica gel 60 F$_{254}$ and by GC-MS using a Shimadzu QP-2010 GC–MS apparatus (Shimadzu Italia s.r.l., Milano, Italy) at 70 eV ionization voltage equipped with a 95% methyl polysiloxane–5% phenyl polysiloxane capillary column (30 m × 0.25 mm, 0.25 μm). Column chromatography was performed on silica
gel 60 (Merck, 70–230 mesh; Merck Life Science s.r.l., Milano, Italy). Evaporation refers to the removal of solvent under reduced pressure. The HRMS spectra were taken on an Agilent 1260 Infinity UHD accurate-mass Q-TOF mass spectrometer (Agilent Technologies Italia s.p.a. Cernusco sul Naviglio, Milano, Italy), equipped with an electrospray ion source (ESI) operated in dual ion mode. Ten microliters of the sample solutions (CH$_2$OH) were introduced by continuous infusion at a flow rate of 200 L min$^{-1}$ with the aid of a syringe pump. Experimental conditions were performed as follows: capillary voltage, 4000 V; nebulizer pressure, 20 psi; flow rate of drying gas, 10 L/min; temperature of sheath gas, 325 °C; flow rate of sheath gas, 10 L/min; skimmer voltage, 60 V; OCT1 RF Vpp, 750 V; fragmentor voltage, 170 V. The spectra data were recorded in the $m/z$ range of 100–1000 Da in a centroid pattern of full-scan MS analysis mode. The MS/MS data of the selected compounds were obtained by regulating diverse collision energy (18–45 eV).

3.2. Preparation of Substrates

Substrates were prepared and characterized as described in the Supplementary Materials.

3.3. General Procedure for the Synthesis of Benzimidazoxazinone Derivatives

See Table 2 for reference. A Schlenk flask was charged under nitrogen with the N-Boc-2-alkynylbenzimidazole 1 (1 mmol) (1a: 298 mg; 1b: 326 mg; 1c: 328 mg; 1e: 367 mg; 1f: 343 mg; 1g: 343 mg; 1h: 354 mg; 1i: 312 mg; 1j: 346 mg; 1k: 338 mg; 1l: 322 mg; 1m, 286 mg; 1n: 328 mg; 1o: 286 mg), anhydrous CH$_2$Cl$_2$ (1 mL), and ZnCl$_2$ (204 mg, 1.5 mmol). The reaction mixture was heated at 40 °C for 3 h. After cooling, the reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL) and water (5 mL) (for 2a-1, 2n, and 2o). Alternatively, after cooling, the solvent was evaporated, and water (20 mL) was added to the residue (for 2m). Phases were separated by washing with CH$_2$Cl$_2$ (5 mL) and CH$_2$Cl$_2$ (3 mL). The eluent (for substrates 1f and 1g) was purified by column chromatography on silica gel 60 (Merck, 70–230 mesh; Merck Life Science s.r.l., Milano, Italy). With phases separated the aqueous phase was washed with CH$_2$Cl$_2$ (3 mL) and CH$_2$Cl$_2$ (5 mL) and the combined organic phases were dried with Na$_2$SO$_4$. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using hexane/AcOEt (8:2, v/v) as the eluent (for 2a-1, 2n, and 2o). For the purification of 2m, the product obtained as the main product was filtered and washed with water (3 × 5 mL) and then purified by column chromatography on silica gel using hexane/AcOEt (8:2, v/v) as eluent. With substrates 1f and 1g, the reaction also led to the formation of deprotected products 3f and 3g, respectively (Scheme 3) (order of elution: 3f followed by 2f; 2g followed by 3g).

3.3.1. 3-Butyl-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2a

Yield: 198 mg, starting from 298 mg of 1a (82%) (Table 2, entry 1). Colorless solid, mp: 92–94 °C; IR (KBr): $v$ = 1759 (s), 1667 (m), 1558 (w), 1450 (m), 1366 (s), 1096 (m), 972 (w), 849 (w), 748 (m) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 8.24–8.13 (m, 1 H, aromatic), 7.82–7.73 (m, 1 H, aromatic), 7.52–7.36 (m, 2 H, aromatic), 6.50 (s, 1 H, H-4), 2.61 (t, $J$ = 7.3, 2 H, =CH$_2$), 1.75 (quint, $J$ = 7.3, 2 H, CH$_2$CH$_2$CH$_3$), 1.46 (hexuplet, $J$ = 7.3, 2 H, CH$_2$CH$_2$CH$_3$), 0.98 (t, $J$ = 7.3, 3 H, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 162.9, 147.4, 144.1, 129.3, 126.3, 124.9, 119.7, 114.6, 96.6, 32.8, 28.4, 22.1, 137; GC/MS = 242 (M$^+$, 100), 227 (2), 213 (3), 200 (42), 185 (31), 171 (6), 158 (43); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{14}$H$_{15}$N$_2$O$_2$: 243.1132; Found: 243.1132.

3.3.2. 3-Butyl-7,8-dimethyl-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2b

Yield: 208 mg, starting from 326 mg of 1b (77%) (Table 2, entry 2). Colorless solid, mp: 133–137 °C; IR (KBr): $v$ = 1768 (s), 1667 (m), 1558 (w), 1450 (m), 1381 (s), 1111 (w), 741 (w) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.92 (s, 1 H, H-6 or H-9), 7.48 (s, 1 H, H-9 or H-6), 6.44 (s, 1 H, H-4), 2.59 (t, $J$ = 7.5, 2 H, =CH$_2$), 2.40 (s, 3 H, CH$_3$ at C-7 or C-8), 2.38 (s, 3 H, CH$_3$ at C-8 or C-7), 1.72 (quint, $J$ = 7.5, 2 H, CH$_2$CH$_2$CH$_3$), 1.44 (hexuplet, $J$ = 7.5, 2 H, CH$_2$CH$_3$), 0.98 (t, $J$ = 7.5, 3 H, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 160.2, 146.6, 144.2, 142.5, 135.3, 134.3, 127.6, 119.8, 114.7, 96.7, 32.8, 28.5, 22.1, 20.4, 13.7; GC/MS = 270 (M$^+$,
3.3.3. 3-Butyl-8-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2c

Yield: 207 mg, starting from 328 mg of 1c (76%) (Table 2, entry 3). Colorless solid, mp: 96–99 °C; IR (KBr): ν = 1767 (s), 1667 (m), 1489 (m), 1443 (w), 1366 (m), 1281 (m), 1204 (w), 1026 (w), 818 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.70 (d, J = 2.5, 1 H, H-9), 7.63 (d, J = 8.8, 1 H, H-6), 7.06 (dd, J = 8.8, 2.5, 1 H, H-7), 6.46–6.44 (m, 1 H, H-4), 2.60 (t, J = 7.5, 2 H, =CCH₂), 1.72 (quint, J = 7.5, 2 H, CH₂CH₂CH₂), 1.45 (hexuplet, J = 7.5, 2 H, CH₂CH₂), 0.98 (t, J = 7.5, 3 H, CH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 167.1, 158.0, 146.3, 144.4, 138.3, 130.2, 120.2, 115.5, 98.3, 96.8, 56.0, 32.8, 28.5, 22.1, 13.7; GC/MS: m/z = 272 (M⁺, 100), 257 (17), 229 (29), 215 (22), 187 (14); HRMS (ESI-TOF) m/z: [M + H⁺] Calcd for C₁₅H₁₇N₂O₃ 273.1234; Found: 273.1237.

3.3.4. 3-Butyl-7-methoxy-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2d

Yield: 226 mg, starting from 328 mg of 1d (83%) (Table 2, entry 4) Colorless solid, mp: 93–97 °C; IR (KBr): ν = 1760 (s), 1658 (m), 1489 (m), 1435 (w), 1366 (m), 1281 (m), 1150 (m), 1103 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.84 (d, J = 8.9, 1 H, H-9), 7.24 (s, 1H, H-6), 7.06–7.00 (m, 1 H, H-8), 6.50–6.47 (m, 1 H, H-4), 2.61 (t, J = 7.5, 2 H, =CCH₂), 1.73 (quint, J = 7.5, 2 H, CH₂CH₂CH₂), 1.45 (hexuplet, J = 7.5, 2 H, CH₂CH₂), 0.98 (t, J = 7.5, 3 H, CH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 162.7, 158.9, 148.0, 145.5, 144.0, 123.5, 114.9, 113.8, 102.7, 96.6, 55.8, 32.8, 28.5, 22.1, 13.7; GC/MS: m/z = 272 (M⁺, 100), 230 (20), 215 (15), 199 (11), 188 (19); HRMS (ESI-TOF) m/z: [M + H⁺] Calcd for C₁₅H₁₇N₂O₃ 273.1234; Found: 273.1242.

3.3.5. 3-Butyl-7,8-dichloro-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2e

Yield: 240 mg, starting from 367 mg of 1e (77%) (Table 2, entry 5). Colorless solid, mp: 143–147 °C; IR (KBr): ν = 1775 (s), 1667 (m), 1543 (w), 1435 (w), 1350 (m), 1134 (w), 1096 (m) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ = 8.18 (s, 1 H, H-6 or H-9), 8.07 (s, 1 H, H-9 or H-6), 6.91 (s, 1 H, H-4), 2.63 (t, J = 7.4, 2 H, =CCH₂), 1.65 (quint, J = 7.4, 2 H, =CCH₂), 1.40 (hexuplet, J = 7.4, 2 H, CH₂CH₂), 0.93 (t, J = 7.4, 3 H, CH₃); ¹³C NMR (125 MHz, DMSO-d₆): δ = 163.9, 150.0, 143.5, 128.7, 128.3, 126.3, 120.5, 114.9, 96.3, 31.8, 27.9, 21.3, 13.5; GC/MS: m/z = 312 [(M + 2)⁺, 61], 310 (M⁺, 100), 268 (25), 253 (22), 226 (31), 202 (6); HRMS (ESI-TOF) m/z: [M + H⁺] Calcd for C₁₅H₁₃Cl₂N₂O₂ 311.0349; Found: 311.0348.

3.3.6. 3-Butyl-8-nitro-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2f

Yield: 129 mg, starting from 343 mg of 1f (45%) (Table 2, entry 6). Colorless solid, mp: 165–168 °C; IR (KBr): ν = 1775 (s), 1659 (m), 1543 (w), 1520 (m), 1343 (m), 748 (w) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 9.05 (d, J = 1.9, 1 H, H-9), 8.39 (dd, J = 8.8, 1.9, 1 H, H-7), 7.83 (d, J = 8.8, 1 H, H-6), 6.63 (s, 1 H, H-4), 2.70 (t, J = 7.4, 2 H, =CCH₂), 1.76 (quint, J = 7.4, 2 H, =CCH₂), 1.49 (hexuplet, J = 7.4, 2 H, CH₂CH₂CH₂), 1.00 (t, J = 7.4, 3 H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 165.6, 151.5, 148.6, 144.7, 143.2, 129.0, 122.1, 119.8, 111.0, 96.6, 33.1, 28.4, 22.1, 13.7; GC/MS: m/z = 287 (M⁺, 100), 257 (11), 245 (49), 230 (27), 203 (23), 184 (16); HRMS (ESI-TOF) m/z: [M + Na + MeOH]⁺ Calcd for C₁₅H₁₂N₂O₃Na⁺ 342.1060; Found: 342.1064.

3.3.7. 3-Butyl-7-nitro-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2g

Yield: 86 mg, starting from 343 mg of 1g (30%) (Table 2, entry 7). Yellow solid, mp: 144–147 °C; IR (KBr): ν = 1775 (s), 1667 (m), 1520 (s), 1350 (s), 1173 (w), 1119 (w), 934 (w), 833 (m), 741 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 8.62 (s, 1 H, H-6), 8.38–8.30 (m, 2 H, H-8 or H-9), 6.60 (s, 1 H, H-4), 2.68 (t, J = 7.4, 2 H, =CCH₂), 1.76 (quint, J = 7.4, 2 H, =CCH₂), 1.49 (hexuplet, J = 7.4, 2 H, CH₂CH₂CH₂), 1.00 (t, J = 7.4, 3 H, CH₃); ¹³C NMR (75 MHz, DMSO-d₆): δ = 164.7, 150.1, 146.4, 144.2, 143.5, 133.5, 120.2, 115.8, 114.7, 96.5, 33.0,
3.3.8. 3-Octyl-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2h

Yield: 254 mg, starting from 354 mg of 1h (85%) (Table 2, entry 8). Colorless solid, mp: 90–94 °C; IR (KBr): v = 1759 (s), 1667 (m), 1551 (m), 1396 (m), 1373 (m), 1134 (m), 1103 (m), 964 (w), 756 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 8.28–8.17 (m, 1 H, aromatic), 7.83–7.75 (m, 1 H, aromatic), 7.50–7.39 (m, 2 H, aromatic), 6.70 (s, 1 H, H-4), 2.62 (t, 6 H, =CCH₂H₂), 1.48–1.18 [m, 10 H, (CH₂)₃CH₂], 0.89 (t, J = 7.0, 3 H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 163.4, 147.8, 143.9, 143.5, 129.1, 126.4, 125.1, 119.5, 114.6, 96.4, 33.2, 31.8, 29.2, 29.1, 28.9, 26.4, 22.6, 14.1; GC/MS: m/z = 286 (M⁺, 85), 283 (2), 269 (4), 255 (5), 239 (5), 225 (14), 215 (100), 200 (87), 185 (40), 171 (11), 158 (61), 130 (20); HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for C₁₉H₁₃N₂O₂⁺ 299.1754; Found: 299.1757.

3.3.9. 3-Isopentyl-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2i

Yield: 210 mg, starting from 312 mg of 1i (82%) (Table 2, entry 9). Colorless solid, mp: 102–104 °C; IR (KBr): v = 1751 (s), 1667 (m), 1551 (w), 1451 (w), 1366 (s), 1134 (m), 1103 (m), 964 (w), 849 (w), 748 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 8.21–8.15 (m, 1 H, aromatic), 7.77–7.72 (m, 1 H, aromatic), 7.50–7.37 (m, 2 H, aromatic), 6.48 (s, 1 H, H-4), 2.65–2.55 (m, 2 H, =CCH₂), 1.73–1.56 (m, 3 H, CH₂CH), 0.96 (d, J = 6.2, 6 H, 2 CH₃), ¹³C NMR (75 MHz, CDCl₃): δ = 163.1, 147.4, 144.1, 144.0, 129.3, 126.2, 126.4, 119.7, 114.9, 96.5, 35.3, 31.1, 27.6, 22.3; GC/MS: m/z = 256 (M⁺, 100), 241 (6), 227 (2), 214 (10), 200 (56), 185 (25), 171 (5), 158 (61), 143 (4), 130 (14); HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for C₁₈H₁₃N₂O₂⁺ 257.1285; Found: 257.1286.

3.3.10. 3-Phenethyl-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2j

Yield: 232 mg, starting from 346 mg of 1j (80%) (Table 2, entry 10). Colorless solid, mp: 159–162 °C; IR (KBr): v = 1767 (s), 1667 (m), 1558 (w), 1451 (w), 1360 (s), 1103 (m), 988 (m), 864 (m), 756 (s), 694 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 8.25–8.17 (m, 1 H, aromatic), 7.81–7.72 (m, 1 H, aromatic), 7.50–7.37 (m, 2 H, aromatic), 6.84 (s, 1 H, H-4), 2.65–2.55 (m, 2 H, =CCH₂), 1.73–1.56 (m, 3 H, CH₂CH), 0.96 (d, J = 6.2, 6 H, 2 CH₃), ¹³C NMR (75 MHz, CDCl₃): δ = 163.4, 147.1, 144.0, 143.9, 139.2, 129.3, 128.7, 128.2, 126.7, 126.3, 125.0, 119.8, 114.6, 97.3, 34.8, 32.5; GC/MS: m/z = 290 (M⁺, 34), 245 (1), 199 (7), 185 (2), 155 (5), 129 (3), 102 (4), 91 (100); HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for C₁₉H₁₅N₂O₂⁺ 299.1128; Found: 299.1126.

3.3.11. 3-(Cyclohexylmethyl)-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2k

Yield: 197 mg, starting from 338 mg of 1k (70%) (Table 2, entry 11). Colorless solid, mp: 135–138 °C; IR (KBr): v = 1767 (s), 1667 (m), 1559 (w), 1451 (m), 1389 (m), 1366 (m), 1096 (w), 964 (w), 748 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.21 (d, J = 7.7, 1 H, aromatic), 7.77 (d, J = 8.1, 1 H, aromatic), 7.52–7.40 (m, 2 H, aromatic), 6.49 (s, 1 H, H-4), 2.48 (d, J = 7.0, 2 H, =CCH₂), 1.93–1.62 (m, 6 H, cyclohexyl), 1.39–0.96 (m, 5 H, cyclohexyl); ¹³C NMR (125 MHz, CDCl₃): δ = 161.6, 147.3, 144.2, 129.4, 126.3, 119.8, 114.6, 97.7, 41.0, 35.8, 33.0, 26.2, 26.0; GC/MS: m/z = 282 (M⁺, 67), 200 (100), 156 (24), 129 (5); HRMS (ESI-TOF) m/z: [M + H]⁺ Calcd for C₂₁H₁₉N₂O₂⁺ 283.1441; Found: 283.1448.

3.3.12. 3-(Cyclohex-1-en-1-yl)-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2l

Yield: 176 mg, starting from 322 mg of 1l (66%) (Table 2, entry 12). Colorless solid, mp: 191–195 °C; IR (KBr): v = 1767 (s), 1636 (m), 1420 (w), 1366 (m), 1281 (w), 1180 (w), 1111 (m), 1026 (w), 833 (w), 748 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 8.24–8.16 (m, 1 H, aromatic), 7.81–7.71 (m, 1 H, aromatic), 7.53–7.39 (m, 2 H, aromatic), 7.00–6.90 (m, 1 H, =CH), 6.55 (s, 1 H, H-4), 2.40–2.24 (m, 4 H, cyclohexyl), 1.86–1.74 (m, 2 H, cyclohexyl), 1.74–1.62 (m, 2 H, cyclohexyl); ¹³C NMR (75 MHz, CDCl₃): δ = 157.7, 148.1, 144.5, 143.6, 134.0, 129.5, 127.1, 126.2, 124.9, 119.6, 114.5, 92.8, 25.9, 23.9, 22.0, 21.5; GC/MS: m/z = 266
3.3.13. 3-(Methoxymethyl)-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2m

Yield: 138 mg, starting from 286 mg of 1m (60%) (Table 2, entry 13). Yellow solid, mp: 122−125°C; IR (KBr): ν = 1751 (s), 1667 (m), 1558 (m), 1443 (m), 1381 (s), 1173 (m), 1103 (s), 957 (w), 748 (s) cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ = 8.23−8.18 (m, 1 H, aromatic), 7.82−7.75 (m, 1 H, aromatic), 7.53−7.43 (m, 2 H, aromatic), 6.81−6.78 (m, 1 H, H-4), 4.35 (s, 2 H, CH₂OCH₃), 3.53 (s, 3 H, OCH₃); 13C NMR (125 MHz, CDCl₃): δ = 158.2, 146.8, 144.1, 143.5, 129.4, 126.4, 125.3, 120.0, 114.6, 97.2, 69.6, 59.4; GC/MS: m/z = 230 (M⁺, 89), 199 (5), 185 (100), 171 (10), 157 (48), 129 (8); HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₁₂H₁₁N₂O₅⁺ 231.0764; Found: 231.0768.

3.3.14. Methyl 3-(1-oxo-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-3-yl)propanoate 2n

Yield: 101 mg, starting from 328 mg of 1n (74%) (Table 2, entry 14). Colorless solid, mp: 189−193°C; IR (KBr): ν = 1767 (s), 1736 (s), 1667 (m), 1435 (w), 1366 (w), 1173 (m), 996 (m), 895 (w), 541 (w), 772 (m) cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ = 8.19 (d, J = 7.7, 1 H, aromatic), 7.77 (d, J = 8.1, 1 H, aromatic), 7.51−7.41 (m, 2 H, aromatic), 6.58 (s, 1 H, H-4), 3.72 (s, 3 H, CO₂CH₃), 2.97 (t, J = 7.2, 2 H, =CH₂), 2.79 (t, J = 7.2, 2 H, CH₂CO₂CH₃); 13C NMR (125 MHz, CDCl₃): δ = 171.8, 160.4, 147.0, 144.1, 143.7, 126.4, 125.2, 119.9, 114.6, 97.5, 52.1, 30.5, 28.4; GC/MS: m/z = 272 (M⁺, 66), 243 (15), 212 (100), 199 (35), 185 (33), 169 (20), 157 (35); HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₁₄H₁₃N₂O₅⁺ 273.0870; Found: 273.0874.

3.3.15. 3-(2-(tert-Butoxy)ethyl)-1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-one 2o'

Yield: 189 mg, starting from 286 mg of 1o (66%) (Table 2, entry 2). Yellow solid, mp: 189−193°C; IR (KBr): ν = 1774 (s), 1666 (m), 1551 (w), 1389 (w), 1386 (m), 1204 (w), 1111 (w), 1080 (m), 756 (m) cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ = 8.25−8.21 (m, 1 H, aromatic), 7.82−7.77 (m, 1 H, aromatic), 7.52−7.42 (m, 2 H, aromatic), 6.65 (t, J = 0.8, 1 H, H-4), 3.73 (t, J = 6.1, 2 H, CH₂OT-Bu), 2.83 (td, J = 6.1, 0.8, 2 H, =CH₂), 1.20 (s, 9 H); 13C NMR (125 MHz, CDCl₃): δ = 160.5, 147.4, 144.2, 144.0, 129.4, 126.3, 125.0, 119.8, 114.6, 98.0, 73.5, 57.7, 34.5, 27.4; GC/MS: m/z = 286 (M⁺, 21), 213 (12), 200 (100), 171 (16), 156 (22); HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₁₄H₁₃N₂O₄⁺ 287.1390; Found: 287.1395.

3.3.16. 2-(Hex-1-yn-1-yl)-6-nitro-1H-benzimidazole 3f

Yield: 49 mg, starting from 343 mg of 1f (20%) (Table 2, entry 6). Colorless solid, mp: 138−140°C; IR (KBr): ν = 2230 (w), 1520 (s), 1474 (w), 1435 (w), 1343 (s), 1065 (w), 818 (m) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆): δ = 8.41 (s, br, 1 H, H-3), 8.14 (dd, J = 8.9, 2.2, 1 H, H-5), 7.69 (d, J = 8.9, 1 H, H-4), 2.58 (t, J = 7.2, 2 H, ≡CH₂), 1.60 (quint, J = 7.2, 2 H, CH₂CH₂CH₃), 1.49 (hexuplet, J = 7.2, 2 H, CH₂CH₂CH₃), 0.95 (t, J = 7.2, 3 H, CH₃) (Note: the NH signal was incorporated into the broad HOD signal at 3.49 ppm); 13C NMR (125 MHz, DMSO-d₆): δ = 143.1, 139.6, 118.3, 114.3 (br), 95.8, 71.6, 29.5, 21.4, 18.1, 13.3; GC/MS: m/z = 243 (M⁺, 100), 228 (48), 214 (73), 201 (93), 182 (41), 168 (54), 155 (57), 127 (27); HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₁₃H₁₄N₃O₂⁺ 244.1081; Found: 244.1081.

3.3.17. 2-(Hex-1-yn-1-yl)-5-nitro-1H-benzimidazole 3g

Yield: 75 mg, starting from 343 mg of 1g (31%) (Table 2, entry 7). Yellow solid, mp: 145−148°C; IR (KBr): ν = 2237 (w), 1520 (s), 1474 (w), 1435 (w), 1366 (w), 1342 (s), 1065 (m), 818 (m), 741 (m) cm⁻¹; 1H NMR (500 MHz, CDCl₃): δ = 8.75 (s, 1 H, H-4), 8.29 (d, J = 8.8, 1 H, H-6), 7.83 (d, J = 8.8, 1 H, H-7), 2.48 (t, J = 7.3, 2 H, ≡CH₂), 1.50 (quint, J = 7.3, 2 H, CH₂CH₂CH₃), 1.33 (hexuplet, J = 7.3, 2 H, CH₂CH₂CH₃), 0.78 (t, J = 7.3, 3 H, CH₃) (Note: the NH signal was too broad to be detected); 13C NMR (125 MHz, CDCl₃): δ = 144.4, 140.4, 119.2, 115.1 (br), 112.6 (br), 98.2, 71.0, 29.9, 22.0, 19.1, 13.4; GC/MS: m/z = 243 (M⁺, 100), 228 (44), 214 (71), 201 (96), 182 (40), 168 (54), 155 (56); HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₁₃H₁₄N₃O₂⁺ 244.1081; Found: 244.1082.
4. Conclusions

In conclusion, we have reported that simple and inexpensive ZnCl\(_2\) is able to promote the heterocyclization of 2-N-Boc-2-alkynylbenzimidazoles under mild conditions (40 °C in CH\(_2\)Cl\(_2\) for 3 h), giving access to new polycyclic heterocycles, 1H-benzo[4,5]imidazo[1,2-c][1,3]oxazin-1-ones. While in the previous literature ZnCl\(_2\) was reported to promote complete N-Boc deprotection with elimination of isobutene and CO\(_2\), in the present process it assisted the 6-endo-dig heterocyclization of the carbamate intermediate with incorporation of the carbamate group into the final polyheterocyclic derivative. ZnCl\(_2\) thus played a dual role, by promoting the Boc deprotection of the substrate with elimination of the tert-butylocarbonation (which could be trapped by substrates bearing a nucleophilic group) and activating the triple bond toward the intramolecular nucleophilic attack by the carbamate moiety. The benzimidazoaxazinone derivatives have been obtained in moderate to high yields starting from differently substituted substrates, and the structure of representative products has been confirmed by X-ray diffraction analysis.

Supplementary Materials: The following are available online. Preparation and characterization of 2-N-Boc-2-alkynylbenzimidazole substrates 1a–1o, X-ray crystallographic data for products 2a, 2c, and 2f, Copies of HRMS, \(^1\)H NMR, and \(^{13}\)CNMR spectra.

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