Synthesis of Diversified Pyrazolo[3,4-b]pyridine Frameworks from 5-Aminopyrazoles and Alkynyl Aldehydes via Switchable C≡C Bond Activation Approaches

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Abstract: A cascade 6-endo-dig cyclization reaction was developed for the switchable synthesis of halogen and non-halogen-functionalized pyrazolo[3,4-b]pyridines from 5-aminopyrazoles and alkynyl aldehydes via C≡C bond activation with silver, iodine, or NBS. In addition to its wide substrate scope, the reaction showed good functional group tolerance as well as excellent regional selectivity. This new protocol manipulated three natural products, and the arylation, alkynylation, alkenylation, and selenylation of iodine-functionalized products. These reactions demonstrated the potential applications of this new method.

Keywords: pyrazolo[3,4-b]pyridine; alkyne activation; regional selectivity; 6-endo-dig cyclization

1. Introduction

A series of natural products and biologically active molecules contain pyrazolo[3,4-b]pyridine as a key structural motif [1,2]. Several of these compounds are effective antivirals, antimalarials, anticancer agents, and kinase inhibitors (Figure 1) [3–5]. This has inspired the development of efficient methods to construct these compounds and has become a hot topic in modern organic synthesis.

Figure 1. Some biologically active pyrazolo[3,4-b]pyridine derivatives.

Recently, catalytic carbon-carbon bond activation has emerged as a useful tool to build complex molecules rapidly and efficiently [6–9]. There are versatile intermediates involved in these reactions, which could be trapped in situ by a second molecule that triggers subsequent tandem reactions [10–15]. The nucleophilic/electrophilic addition reactions of alkynes are well-known and provide a convenient way to synthesize functionalized molecules [16–20]. The high reactivity, good selectivity, excellent functional-group tolerance,
and mild reaction conditions of these reactions have inspired significant research over the past few decades. Generally, this process forms highly active intermediates using transition metals, such as Ag, Au, Rh, Cu, and Co [21–27], or electrophiles like I₂, NXS (X = I, Br, Cl), Se, S, and P (Scheme 1a) [28–34]. Each reagent type sees significant use in the development of synthetic methodologies and applications to prepare bioactive compounds or complex naturally occurring skeletons. However, to our knowledge, among those strategies, a direct and efficient protocol for the selective synthesis of polysubstituted and functionalized fused heterocycles, such as halogen-functionalized pyrazolo[3,4-b]pyridine frameworks, by C≡C bond activation has seldom been described. Thus, developing convenient and sustainable synthetic methods to build these high-value compounds merits attention.

Scheme 1. Strategies for the synthesis of diverse molecules via activating C≡C bond.

As a kind of synthetic block with bifunctional groups (C≡C and carbonyl), alkynyl aldehydes are essential synthons with rich and unexpected chemical properties [35–38]. Tandem cyclization reactions using alkynyl aldehydes as synthons yields a variety of heterocycles. Generally, tandem cyclization occurs in one of two ways, 5-exo-dig or 6-endo-dig cyclizations. For example, some efficient synthesis strategies have been reported for the synthesis of multi-substituted thiazoles, imidazo[1,2-a]pyridines, and imidazoles by using alkynyl aldehydes as synthons via 5-exo-dig cyclization [39–41]. The 6-endo-dig cyclization of alkynyl aldehydes is an alternative method to construct complex fused ring systems (Scheme 1b) [42–44]. These protocols typically use simple starting materials, with good functional tolerance and high yields. Inspired by these achievements, we sought to selectively activate the C≡C bond by changing the reaction conditions to obtain a series of compounds with a pyrazolo[3,4-b]pyridine structure core.

2. Results and Discussion

To evaluate our idea, we chose 3-methyl-1-phenyl-1H-pyrazol-5-amine (1a) and 3-phenylpropionaldehyde (2a) as the model substrates for the optimization of the conditions. Through optimization of the catalyst, additive, solvent and temperature, the optimal reaction conditions can be summarized as follows: 1a (0.2 mmol) and 2a (0.2 mmol) in DMAc (1.5 mL) with Ag(CF₃CO₂) (10 mol%), TfOH (30 mol%), at 100 °C for 2 h (details appear in Supplementary Materials Tables S3–S6).

Having optimized the reaction conditions, we determined the versatility of this reaction. We examined a series of 5-aminopyrazole derivatives to test the generality of this method and evaluate the electronic influence of aromatic ring substitutions. As shown in
Scheme 2, pyrazole rings bearing electron-donating groups (e.g., 3-Me, 3-(t-Bu), 1-Ph, 3-Ph) led to good yields (74–84%) of the corresponding products (3a–3d and 3f–3k). Notably, the structure of compound 3a was confirmed by X-ray single-crystal diffraction (Scheme 2). The substrates of aromatic rings attached to halogen atoms (e.g., 4-F, 4-Br) also led to their corresponding products (3e and 3l–3p) in yields between 68–81%. A strongly electron-deficient substrate was applied and afforded its product in 63% yield for the corresponding product 3q. Pyrazole rings only bearing alkyl groups were used as starting materials and yielded the expected products (3r–3t) in moderate to good yields (66–75%). Additionally, 5-aminoisoxazoles also readily reacted with 3-phenylpropionaldehyde, yielding the desired products (3u–3x) in good yields (70–75%). However, 3-methylisothiazol-5-amine did not yield the desired product 3y.

Scheme 2. Substrate scope and Isolated yield of substituted 5-aminopyrazoles and derivatives. Reaction conditions: 1 (0.2 mmol), 2a (0.2 mmol), Ag(CF₃CO₂) (10 mol%), TfOH (30 mol%) in DMAc (1.5 mL) at 100 °C for 2 h. c N.D. = not detected.
We next investigated the scope of alkynyl aldehydes derivatives for this reaction (Scheme 3). First, we examined 3-phenylpropioaldehydes with phenyl rings containing electron-rich substituents (e.g., 4-Me, 4-Et, 4-OMe, 4-OEt, 3,4-(OMe)2). Annulation reactions occurred smoothly to deliver products (4b–4f) in 64–78% yields. For 3-phenylpropioaldehyde containing electron-withdrawing groups (e.g., 4-Ac, 4-CO2Me, 4-CF3, 4-F, 3-F, 3-Cl, 4-Br), the reaction proceeded smoothly and afforded products (4g–4i and 4l–4o) in moderate to good yields (66–81%). In addition, when 4-phenylbut-2-ynal and 3-(trimethylsilyl)propioaldehyde were used as starting materials, products 4j and 4k were obtained in good yields (67% and 73% respectively). It is worth noting that when using 3-(trimethylsilyl)propioaldehyde, compound 4k was the product of the trimethylsilyl group removal. Furthermore, different heterocyclic aldehydes were also investigated including furan, thiophene, and pyridine to generate products 4p–4s in 65–72% yields. We were delighted to find that alkyl alkynyl aldehydes gave the corresponding products 4t–4u in moderate yields as well.

Scheme 3. Substrate scope and Isolated yield of substituted alkynyl aldehydes and derivatives. Reaction conditions: 1a (0.2 mmol), 2 (0.2 mmol), Ag(CF3CO2) (10 mol%), TfOH (30 mol%) in DMAc (1.5 mL) at 100 °C for 2 h.

The iodinated product was detected when 1.0 equivalent of iodine was added to the reaction system (control experiment, Scheme 7d). We chose 1a and 2a as model substrates to investigate the optimal conditions to synthesize iodinated products (more details appear in Supplementary Materials Tables S7 and S8).

Next, various 5-aminopyrazoles and alkynyl aldehydes were tested to determine the scope of iodine-functionalized products (Scheme 4). These reactions produced the corresponding products 5a–5j in 58–68% yields. Meanwhile, 3-methylisoxazol-5-amine tolerated the reaction conditions and reacted with 3-phenylpropioaldehyde (2a) to generate 5k in moderate yield. When iodine was replaced by NBS, the expected compounds 5l–5r were obtained in moderated yields (53–66%). However, after many trials, the Cl-functionalized product 5s was not obtained.
Scheme 4. The substrate scope and isolated yield of halogen-functionalized products. Reaction conditions: 1 (0.2 mmol), 2 (0.2 mmol), I\textsubscript{2} or NBS (2.0 equiv.), TfOH (1.0 equiv.) in DMSO (2 mL) at 100 °C for 6 h. \textsuperscript{c} N.D. = not detected.

To demonstrate the applicability of this method, we modified natural products (Scheme 5a). For example, estrone, formononetin, and eudistomin \(\text{Y}_1\) are all biologically active natural products, and these compounds have phenolic hydroxyl groups that undergo conversion into trifluoromethane sulfonates. Those sulfonates undergo Sonogashira coupling and deketalization to afford alkynaldehyde intermediates (6, 8, and 10). By using these alkynaldehyde intermediates as substrates for this protocol, we successfully obtained three natural product functionalized pyrazolo[3,4-\(b\)]pyridines in moderate to good yields (7, 9, and 11). Because heteroaryl iodides are highly useful functional structures in synthetic organic chemistry, additional applications of iodine-functionalized products were conducted (Scheme 5b) \[45\]. A series of coupling reactions were examined to form iodine-functionalized products, including Suzuki, Sonogashira, and Heck couplings that yielded the expected products 13–15 in good yields. Furthermore, selenization of iodine-functionalized products afforded 16 in very good yield (78%).
Scheme 5. Strategies to synthesize diverse molecules via C≡C bond activation.

The reaction of 1a and 2a was scaled up to 5 mmol to illustrate the potential applications of this method; 3a and 5a formed 71% and 53% yields, respectively (Scheme 6). This promising result lays a good foundation for large-scale syntheses.

Relevant control experiments were conducted to probe the reaction mechanism for the formation of pyrazolo[3,4-b]pyridine frameworks. When the reaction of 1a with 2a was conducted without acid for 2 h, it afforded 3a and 3a′ in 40% and 46% yields, respectively, (Scheme 7a). Intermediate 3a′ was confirmed by TLC-MS(APCI), LC-HRMS, and NMR (the details can be seen in Supplementary Materials). In addition, intermediate 3a′ transform to 3a in 88% yield under standard conditions (Scheme 7b). These results suggested that 3a′ may serve as the intermediate in this reaction. To illustrate regioselectivity, we chose cinnamaldehyde (2a′) as a substrate to react with 1a under standard conditions. Compared with a standard simple, 3-methyl-1,4-diphenyl-1H-pyrazolo[3,4-b]pyridine (17) was obtained in 45% yield, no product 3a was observed (Scheme 7c). These results confirmed the regioselectivity of this method, as it only afforded the C6 substituted pyrazolo[3,4-b]pyridine for alkynyl aldehydes substrates. Furthermore, when 1 eq. of iodine was added, non-iodinated and iodized products 3a and 5a were detected in 46% and 30% yields, respectively (Scheme 7d).
Scheme 7. Control experiments. (a) Form intermediate 3a’.
(b) Intermediate 3a’ transform to 3a under standard conditions. (c) Validation of regioselectivity experiments. (d) Add one equivalent of iodine under standard conditions.

Considering the aforementioned control experiments and earlier works [46–48], a reaction mechanism is shown in Scheme 8 using 1a with 2a as a typical reaction. Initially, 3-methyl-1-phenyl-1H-pyrazol-5-amine (1a) undergoes condensation with 3-phenylpropionaldehyde (2a) to form intermediate 3a’. Next, the silver salt coordinates to the alkyne of 3a’ to form intermediate A; this undergoes 6-endo-dig cyclization to form B. Finally, B undergoes demetallation to afford product 3a (Scheme 8, pathway A). Similarly, I$_2$ or NBS adds to a triple bond that leads to intermediate A’, which undergoes 6-endo-dig cyclization to form B’, followed by acid loss from B’ to obtain 5a or 5l (Scheme 8, pathway B).

Scheme 8. Plausible mechanistic pathway.

3. Materials and Methods
3.1. General Information
Aminopyrazoles and NBS were purchased from Shanghai Shaoyuan Co. Ltd. (Shanghai, China) 3-substituted propionaldehyde and Ag(CF$_3$CO)$_2$ were purchased from Leyan. Unless stated otherwise, all solvents and commercially available reagents were obtained from commercial suppliers and used without further purification. In addition, petroleum ether (b.p. 60–90°C) was distilled prior to use for Column chromatography. Non-commercial starting materials were prepared as described below or according to literature procedures. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Advance 400 MHz spectrometer at ambient temperature using the non or partly deuterated solvent as internal standard ($^1$H: $\delta$ 7.26 ppm and $^{13}$C[$^1$H]:...
δ 77.0 ppm for CDCl₃; δ 2.50 ppm and 13C{1H}: δ 40.0 ppm for DMSO-d₆). Chemical shifts (δ) are reported in ppm, relative to the internal standard of tetramethylsilane (TMS). The coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or combinations thereof. High resolution mass-spectrometric (HRMS) were obtained on an Apex-Ultra MS equipped with an electrospray source. Melting points were determined using SGW X-4 apparatus and not corrected. The X-ray diffraction data for the crystallized compound were collected on a Bruker Smart APEX CCD area detector diffractometer (graphite monochromator, Mo Kα radiation, λ = 0.71073 Å) at 296(2) K. All the heating procedures were conducted with an oil bath.

3.2. Synthetic Procedures

Typical Procedure (TP 1) for the Synthesis of 3 and 4 Taking 3a as an Example. A 25 mL pressure vial was charged with 1a (34.6 mg, 0.20 mmol, 1.0 equiv.), 2a (26 mg, 24.5 uL, 0.20 mmol, 1.0 equiv.), Ag(CF₃CO₂) (4.4 mg, 0.02 mmol, 10 mol%), TfOH (9 mg, 5.3 uL, 0.06 mmol, 30 mol%) and DMAc (1.5 mL). The vial was sealed and the reaction mixture was stirred at 100 °C for 2 h under air atmosphere (monitored by TLC). After the reaction was completed, and added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The solution was dried over anhydrous Na₂SO₄, concentrated under reduced pressure, and dried under vacuum. The residue was purified by flash column chromatography by using ethyl acetate/petroleum ether mixture to obtain the corresponding product 3a.

Typical Procedure (TP 2) for the Synthesis of 5 Taking 5a as an Example. A 25 mL pressure vial was charged with 1a (34.6 mg, 0.20 mmol, 1.0 equiv.), 2a (26 mg, 24.5 uL, 0.20 mmol, 1.0 equiv.), I₂ (101.5 mg, 0.40 mmol, 2.0 equiv.), TfOH (30 mg, 17.6 uL, 0.20 mmol, 1.0 equiv.) and DMSO (2.0 mL). The vial was sealed, and the reaction mixture was stirred at 100 °C for 6 h under air atmosphere (monitored by TLC). After the reaction was completed, and added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% Na₂S₂O₃ solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography by using ethyl acetate/petroleum ether mixture to obtain the corresponding product 5a.

General Procedure for Synthesis of 13. K₂CO₃ (0.4 mmol, 2.0 equiv.), phenylboronic acid (0.26 mmol, 1.3 equiv.) and PdCl₂(PPh₃)₂ (5 mol%) were added to a solution of 5a (0.2 mmol, 1.0 equiv.) in a 5:1 solvent mixture of dioxane and water. The reaction mixture was heated to 90 °C and stirred at this temperature until complete consumption of 5a was observed (monitored by TLC). After cooling to room temperature, the mixture was diluted with a mixture of EA and water and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine and dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography by using ethyl acetate/petroleum ether mixture to obtain the desired product 13 in 88% yield.

General Procedure for Synthesis of 14. 5a (0.2 mmol, 1 equiv.), PdCl₂(PPh₃)₂ (5 mol%), CuI (10 mol%) and phenylacetylene (0.3 mmol, 1.5 equiv.) were added to a 25 mL Schlenk flask with a stir bar under an Ar atmosphere. Then DMF (2 mL) and TEA (1 mL) were added sequentially. The reaction mixture was then stirred at 90 °C. Afterwards 15 mL of water were added, and the reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine and dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography by using ethyl acetate/petroleum ether mixture to obtain the desired product 14 in 85% yield.

General Procedure for Synthesis of 15. 5a (0.2 mmol, 1 equiv.), Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%) and ethyl acrylate (0.3 mmol, 1.5 equiv.) were added to a 25 mL Schlenk flask with a stir bar under an Ar atmosphere. Then dioxane (2 mL) and TEA (1 mL) were added sequentially. The reaction mixture was then stirred at 90 °C. Afterwards 50 mL of water were added, and the reaction mixture was extracted with EtOAc (3 × 50 mL).
The combined organic fractions were washed with brine and dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography by using ethyl acetate/petroleum ether mixture to obtain the desired product 15 in 75% yield.

**General Procedure for Synthesis of 16.** Adapting a literature procedure [49], a 25 mL Schlenk flask with a stir bar was charged with 5a (0.2 mmol, 1.0 equiv.), diphenyl diselenide (0.14 mmol, 0.7 equiv.) CuI (0.02 mmol, 10 mol%) and Cs₂CO₃ (0.4 mmol, 2.0 equiv.) in MeCN (2.0 mL). The vial was sealed and the resulting mixture was stirred at 80 °C for 24 h under an Ar atmosphere. After the reaction completed, and added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography by using ethyl acetate/petroleum ether mixture to obtain the desired product 16 in 78% yield.

### 4. Conclusions

In summary, a cascade 6-endo-dig cyclization reaction was developed for the switchable synthesis of halogen and non-halogen-functionalized pyrazolo[3,4-b]pyridines from 5-aminopyrazoles and alkynyl aldehydes. This method afforded diversified pyrazolo[3,4-b]pyridine frameworks via C≡C bond activation with silver, iodine, or NBS. The protocol was characterized by a wide substrate scope, good functional group tolerance, and excellent regional selectivity. The structural modification of estrone, formononetin, and eudistomin Y1 provided new ideas for syntheses of drug molecules. Iodine functionalization allowed several additional transformations, including arylation, alkenylation, alkynylation, and selenization to fabricate useful molecules.

### 5. Patents

A patent (Yantai University, CN 112300157, and 2021 A) has been derived from this manuscript. The patent is entitled Novel pyrazolopyridine compound with antitumor activity and preparation method thereof.

**Supplementary Materials:** The following supporting information can be downloaded at: [https://www.mdpi.com/article/10.3390/molecules27196381/s1](https://www.mdpi.com/article/10.3390/molecules27196381/s1). Characterization data for product 3, 4, 5, 6–11, and 13–17, include 1H- and 13C-NMR spectroscopies are available online. CCDC 2075351 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033. References [50–56] are cited in the Supplementary Materials.

**Author Contributions:** Conceptualization, Y.-P.Z.; methodology, Y.-P.Z.; investigation, X.-Y.M. and Y.-J.H.; data curation, F.-R.L. and D.S.; writing—original draft preparation, X.-Y.M., Y.-J.H. and Y.-Y.S.; writing—review and editing, Y.-P.Z.; visualization, F.-R.L.; supervision, A.-X.W. and Y.-P.Z.; project administration, Y.-P.Z. All authors have read and agreed to the published version of the manuscript.

**Funding:** The authors also thank Talent Induction Program for Youth Innovation Teams in Colleges and Universities of Shandong Province. This work was supported by Science and Technology Innovation Development Plan of Yantai (2020MSGY114) and Yantai “Double Hundred Plan”.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** The authors also thank Talent Induction Program for Youth Innovation Teams in Colleges and Universities of Shandong Province. Xue-Han Li, Le-Yang Guan, Yu-Ting Han, Meng-Jiao Lei and Jia-Xin Chen are thanked for purification of some compounds.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Sample Availability:** Samples of the compounds 3, 4, and 5 are available from the authors.
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