Silver-Catalyzed Cascade Cyclization of Amino-NH-1,2,3-Triazoles with 2-Alkynylbenzaldehydes: An Access to Pentacyclic Fused Triazoles

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Abstract: An operationally simple Ag(I)-catalyzed approach for the synthesis of isoquinoline and quinazoline fused 1,2,3-triazoles was developed by a condensation and amination cyclization cascade of amino-NH-1,2,3-triazoles with 2-alkynylbenzaldehydes involving three new C-N bond formations in one manipulation, in which the group of -NH of the triazole ring serves as a nucleophile to form the quinazoline skeleton. The efficient protocol can be applied to a variety of substrates containing a range of functional groups, delivering novel pentacyclic fused 1,2,3-triazoles in good-to-excellent yields.

Keywords: cascade; cyclizations; fused 1,2,3-triazoles; isoquinoline; quinazoline

1. Introduction

Broad attention has been paid to 1,2,3-triazole-containing heterocycles, which have been widely applied in the fields of medicine [1–5], pesticide [6–10], biochemistry [11–14], and material science [15–20] since the ‘Click’ triazole chemistry was founded at the beginning of this century [21,22]. For instance, some of the well-known drugs bearing triazole moiety are presented in Figure 1, including A (Cefatrizine) and B (Tazobactum) as β-lactam antibiotic [1,23–27], C as anti-cancer reagent [23,28], D as potential nonpeptidic angiotensin (II) receptor antagonists [29,30], E as a toll-like receptor [29,31], F as a mental disorders medicine [32], and G as a wall teichoic acid active antibiotic [11].

Figure 1. Some 1,2,3-triazole-based drugs and bioactive molecules.

Owing to these pharmaceutical and biological properties, the constructions of various 1,2,3-triazoles are of paramount significance. The 4-monosubstituted 1,2,3-triazoles play...
remarkable roles in the triazole family [32–41]. Though the main access to this kind of compound, referring to the cycloaddition reaction of acetylene or its substitute with an azide source [42–47], could deliver respectable structures, the variations with the core are far from enough. So, direct modifications of the triazole ring, using its -NH moiety to expand diversity, attract broad attention. Over past decades, most work focused on one C-N bond formation process, especially on $N^2$ of the heterocycle [32–35,39,48–58]. In early 2011, Buchwald demonstrated a Pd-catalyzed selective C-N coupling of 4-monosubstituted 1,2,3-triazoles with aryl bromides, delivering a series of arylated structures, 2,4-disubstituted 1,2,3-triazoles [33], which could not be obtained by traditional cycloaddition reactions. Later, Chen et al. reported a highly $N^2$-selective C-N coupling using pyrrole or indole as an arylation reagent using $N$-iodophthalimide [34] or $N$-iodosuccinimide [48] as a mediator. Vinylation of the $N^2$ was also explored by Shi et al. through Au-catalyzed alkyne activation with about 80% selectivity [49] (Scheme 1a(I)). Meanwhile, $N^2$-selective allylation and benzylolation were investigated, employing allenamide [50], aryldiazoacetate [32], and conjugate olefine (ketone) [51,52] as a reaction partner, respectively. Moreover, the $N^2$-selective alkylation could be also achieved through an additional reaction of the $N(H)$ group with (conjugate) alkene (ketone) [35,39,53,54] or by substitution with epoxide [55], dialkylamide [56], and alcohol [57] (Scheme 1a(II)). Additionally, Reddy et al. realized a highly regioselective $N^2$-sulfonylation of 4-aryl-NH-1,2,3-triazoles with sodium sulfinate or thiosulfonate as a sulfonylation agent, mediated by I$_2$ [58] (Scheme 1a(III)).

**Scheme 1.** Modifications of the NH-1,2,3-triazoles via C-N bond formation. (a) One bond formation to substituted 1,2,3-triazoles; (b) Two bonds formation to tricyclic fused 1,2,3-triazoles; (c) Three bonds formation to pentacyclic fused 1,2,3-triazoles.
Compared to the numerous \( N^2 \)-selective functionalizations, modifications on \( N^1 \) and \( N^3 \) of the 4-monosubstituted 1,2,3-triazoles are much more rare. In 2020, Ma group reported a Cu-catalyzed site- and enantio- selective ring opening of cyclic diaryliodoniums, delivering \( N^1 \)-arylation products of 1,4-disubstituted-1,2,3-triazoles [40] (Scheme 1a(IV)). Maddani et al. reached a selective \( N^1 \)-benzylation by 1,6-addition of the -NH to para-quinone methides mediated by acid of \( \text{CICH}_2\text{CO}_2\text{H} \) [51]. Breit developed a rhodium-catalyzed asymmetric \( N^1 \)-selective alkylation of triazole derivatives with internal alkynes and terminal alkenes [36]. Very recently, Ji et al. reported a selective \( N^1 \)-alkylation of azoles through a three-component process involving ketones as alkylation reagents and \( N,N^2 \)-dimethylpropionamide as a carbon source [59] (Scheme 1a(V)). The \( N^3 \)-selective couplings of the 1,2,3-triazoles were demonstrated by Taylor and Li et al. with vinyl ketone (catalyzed by borinic acid) and alkyne (promoted by TBAF), delivering 1,5-disubstituted derivatives, respectively [60,61] (Scheme 1a(VI)).

In addition to the above one-bond-formation processes, cascade strategies to construct novel and diverse fused structures are more valued and important themes in organic synthesis. In 2013, Shi et al. [62] designed 4-(ortho-halo-aryl) 1,2,3-triazoles to merge with activated nitriles, forming a series of 5-amino-[1,2,3]triazolo-[5,1-\( a \)]isoquinoline derivatives, a kind of valued tricyclic fused 1,2,3-triazoles (Scheme 1b). Though some achievements were reached in this field, there is still a lack of strategies for constructing interesting and complex fused 1,2,3-triazole derivatives, which attracts us considerably as we are persistently interested in this area [63–70]. Sparked by the vigorous performance of 2-alkynylbenzaldehyde in the synthesis of fused cyclic compounds [71–79], herein, we designed 2-(1H-1,2,3-triazol-5-yl)anilines 1 to react with 2-alkynylbenzaldehydes 2 to construct isoquinolinolino [2,1-\( a \)] [1–3] triazolo [1,5-c] quinazolines 3 through a cascade process involving three C-N bond formations in one manipulation. This method features high efficiency, excellent atom economy, and only green by-products of \( \text{H}_2\text{O} \) (Scheme 1c).

2. Results and Discussion

At the outset of our studies, the cascade reaction between 2-(1H-1,2,3-triazol-5-yl)aniline 1a and 2-alkynylbenzaldehyde 2a was investigated as a model (Table 1). To our delight, the reaction proceeded very successfully in the presence of 10 mol\% \( \text{AgNO}_3 \) at 80 °C for 1 hour using DMF as a solvent, delivering the product isoquinolinolino [2,1-\( a \)] [1–3] triazolo [1,5-c] quinazoline 3aa with excellent yield (82%) (Entry 1). The structure of 3aa was unambiguously confirmed by X-ray crystallography analysis (CCDC NO: 2133327) (see Supplementary Materials) [80]. The screening of solvents was then performed. Unfortunately, we found that other solvents, including toluene, DCE, MeCN, and DMSO, were less effective than DMF (Entries 2–5). Increasing or decreasing the temperature of the reaction could not lead to any further improvements in the yield (Entries 6–8). Changing the catalyst to AgOTf resulted in a slightly decreased yield, and the desired product 3aa was obtained with 76% yield (Entry 9). However, the reaction proceeded very reluctantly in the presence of other catalysts (\( \text{Ag}_2\text{O}, \text{Ag}_2\text{CO}_3 \), and AgOAc, without any target molecules detected (Entry 10–12)). When CuSCN or Cul is used instead of \( \text{AgNO}_3 \), the yield drops sharply (Entry 13–14). However, the yield of the reaction slightly decreased when different amounts of \( \text{AgNO}_3 \) catalyst were used (Entry 15–17). After testing different reaction concentrations, 0.2 M DMF was kept as the optimum one (Entry 18–19). Lastly, when the reaction time was extended to 2 hours, the target product was obtained in excellent 92% yield (Entry 20).

With the optimized reaction conditions in hand (Table 1, entry 18), the substrate scope of the cascade cyclization reaction was investigated with \( o \)-alkynyl aldehydes first. To our delight, a variety of \( o \)-alkynyl aldehydes with different alkynyl bearing substituted groups (including various aryl, alkyl, and heteroaryl) could work efficiently with 2-(1H-1,2,3-triazol-5-yl)aniline (1a), as shown in Figure 2. Reactions of 2-alkynylbenzaldehydes containing electron-donating (3ab–3af) and electron-withdrawing (3ag–3al) groups on the phenyl ring proceeded smoothly to afford the corresponding products in moderate-to-good yields (37–88%). Generally, electron-donating groups substituted with alkynylbenzaldehyde
(3ab–3af) were more successfully converted into target products than those with strong electron-withdrawing groups (3ak–3al). It should be noted that alkynylarylaldehyde with 2-pyridyl (3aq) was also suitable for this reaction, furnishing the corresponding products in satisfactory yield. Unfortunately, to substrates with aliphatic groups, such as pentyl, methoxymethyl, and hydroxymethyl on the 2-position of the alkynyl moiety (3an–3ap), the reaction could not provide the desired product. Surprisingly, when 2-((trimethylsilyl)ethynyl)benzaldehyde 2m was used, the desilylation product (3am) was obtained in a low yield of 16%. Then, the effects of substituents on the core benzene ring linked directly to the formyl group were also studied. It was found that both electron-rich (–Me and –OMe) and -poor (–F, –Cl, and –CF3) groups were well tolerated in the reactions, and good yields were obtained (3ar–3av).

Table 1. Optimization of the reaction conditions a.

| Entry | Sol. (x mL) | Temp. (°C) | Cat. (x mol%) | Yield (%) b |
|-------|-------------|------------|---------------|-------------|
| 1     | DMF (2)     | 80         | AgNO3 (10)    | 82          |
| 2     | Toluene (2) | 80         | AgNO3 (10)    | trace       |
| 3     | DCE (2)     | 80         | AgNO3 (10)    | 79          |
| 4     | MeCN (2)    | 80         | AgNO3 (10)    | 70          |
| 5     | DMSO (2)    | 80         | AgNO3 (10)    | 74          |
| 6     | DMF (2)     | 60         | AgNO3 (10)    | 74          |
| 7     | DMF (2)     | 100        | AgNO3 (10)    | 75          |
| 8     | DMF (2)     | 120        | AgNO3 (10)    | 70          |
| 9     | DMF (2)     | 80         | AgOTf (10)    | 76          |
| 10    | DMF (2)     | 80         | Ag2O (10)     | ND          |
| 11    | DMF (2)     | 80         | Ag2CO3 (10)   | ND          |
| 12    | DMF (2)     | 80         | AgOAc (10)    | ND          |
| 13    | DMF (2)     | 80         | CuSCN (10)    | 22          |
| 14    | DMF (2)     | 80         | CuI (10)      | 30          |
| 15    | DMF (2)     | 80         | AgNO3 (5)     | 72          |
| 16    | DMF (2)     | 80         | AgNO3 (20)    | 79          |
| 17    | DMF (2)     | 80         | AgNO3 (30)    | 80          |
| 18    | DMF (1)     | 80         | AgNO3 (10)    | 83          |
| 19    | DMF (4)     | 80         | AgNO3 (10)    | 77          |
| 20 c  | DMF (1)     | 80         | AgNO3 (10)    | 92          |

a Reaction conditions: 1a (0.2 mmol), 2a (0.2 mmol), 1 hour. b Isolated yield. c Reaction time, 2 h.

To gain further insight into the reaction, we continued our study by examining the 2-(1H-1,2,3-triazol-5-yl)aniline substrate scope, as shown in Figure 3. Gratifyingly, different electron-withdrawing group (–F, –Cl, –Br, –CN) and electron-donating group of –Me on 4- or 5-position of the phenyl ring (3ba–3ja) were perfectly tolerated, with the corresponding products obtained in moderate-to-good yields (60–88%).

To illustrate the synthetic applicability of the protocol, the reaction was conducted on a gram-scale. A reaction of 5 mmol of 1a and 2a in 25 mL of DMF was carried out, and it could proceed smoothly under the optimized conditions to produce the product 3aa in 92% (1.60 g) yield within 2 h (Scheme 2).
Figure 2. Scope of 2-alkynylbenzaldehyde. Reaction conditions: 1a (0.2 mmol), 2 (0.2 mmol), AgNO$_3$ (10 mol%) in DMF (1 mL) at 80 °C for 2 h. Isolated yield. $^a$ AgBF$_4$ instead of AgNO$_3$. 
To gain further insight into the reaction, we continued our study by examining the possibilities may exist for the formation of compound 3aa is presented in Scheme 3. The condensation reaction of 2-(1H-1,2,3-triazol-5-yl)aniline 1a and 2-alkynylbenzaldehyde 2a gives an imine in which the C≡C bond coordinates to AgNO₃ catalyst to generate intermediate 4. Then, two possibilities may exist for the formation of compound 3aa. In path A, intermediate 4 would first undergo the intramolecular nucleophilic attack of the 1,2,3-triazole’s N³ atom onto the imine carbon center to form intermediate 5 (the first amination). Intramolecular proton transfer then occurred, producing fused tricyclic intermediate 6, which would undergo a second intramolecular nucleophilic attack of the =NH group onto the triple bond, upon the π-activation by AgNO₃, to afford 7 (the second (hydro-) amination), then deliver the desired compound 3aa through protonolysis. Alternatively (path B), from the N-nucleophilic attack of the imine to the triple bond activated by AgNO₃, imine cation intermediate 5’ could be formed initially, followed by intramolecular nucleophilic attack of triazole’s N³ to the
carbon center of the formed imine to produce the fused pentacyclic intermediate $6'$, which would then give the final compound 3aa through the subsequent deprotonation.

Scheme 3. Proposed mechanism.

3. Materials and Methods

3.1. Synthesis of Various Substituted 2-(1H-1,2,3-Triazol-5-yl) Aniline (Take 1a as An Example) [81,82]

A 15 mL flask equipped with a magnetic stir bar was charged with 2-iodoaniline S1 (2 mmol), trimethylsilylacetylene S2 (3 mmol), bis(triphenylphosphine)palladium (II) chloride (1 mol%), cuprous iodide (5 mol%), and 5 mL of triethylamine. The solution was stirred at room temperature under argon for 12 h. Upon completion of the reaction, the solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel (EtOAc:Petal = 1:50), giving the pure product S3 (Scheme 4).

A 15 mL flask equipped with a magnetic stir bar was charged with 2-((trimethylsilyl)ethynyl)aniline S3 (2 mmol), potassium carbonate (4 mmol), and 5 mL of methanol. The solution was stirred at room temperature for 4 h. Upon completion of the reaction, the mixture was added to H$_2$O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (3 × 5 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure to afford product S4 (Scheme 4).

A 15 mL flask equipped with a magnetic stir bar was charged with 2-ethynylaniline S4 (2 mmol), TMSN$_3$ S5 (3 mmol), cuprous iodide (5 mol%), and 5 mL of mixed solvent (DMF/MeOH = 9/1). The solution was stirred at 100 °C under argon for 12 h. Upon completion of the reaction, the mixture was added to H$_2$O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (3 × 5 mL),
dried over Na₂SO₄, and concentrated under reduced pressure to afford a crude product. Purification by column chromatography on silica gel (EtOAc:Petrol = 1:3) afforded the pure product 1a (Scheme 4).

### Scheme 4. Synthesis of substrate 1a.

#### 3.2. Synthesis of Various Substituted 2-(Phenylethynyl)benzaldehyde (Take 2a as An Example) [83]

A 15 mL flask equipped with a magnetic stir bar was charged with 2-bromobenzaldehyde S6 (2 mmol), phenylacetylene S7 (3 mmol), bis(triphenylphosphine)palladium (II) chloride (1 mol%), cuprous iodide (5 mol%), and 5 mL of triethylamine. The solution was stirred at 80 °C under air for 2 h. Upon completion of the reaction, the mixture was added to H₂O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (3 × 5 mL), dried over Na₂SO₄, and concentrated under reduced pressure to afford a crude product. Purification by column chromatography on silica gel (EtOAc:Petrol = 1:3) afforded the desired product 2a (Scheme 5).

### Scheme 5. Synthesis of substrate 2a.

#### 3.3. General Procedure for Synthesis Pentacyclic Fused Triazoles (Take 3aa as An Example)

A 15 mL flask equipped with a magnetic stir bar was charged with 2-(1H-1,2,3-triazol-5-yl)aniline 1a (0.2 mmol), 2-alkynylbenzaldehyde 2a (0.2 mmol), and 1 mL of DMF. The solution was stirred at 80 °C under air for 2 h. Upon completion of the reaction, the mixture was added to H₂O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (3 × 5 mL), dried over Na₂SO₄, and concentrated under reduced pressure to afford a crude product. Purification by column chromatography on silica gel (EtOAc:Petrol = 1:3) afforded the desired product 3aa.

### 4. Conclusions

In summary, we developed a cascade process of condensation/in-situ generated imine and alkyne aminations of 2-(1H-1,2,3-triazol-5-yl)anilines with 2-alkynylbenzaldehydes catalyzed by AgNO₃ to deliver novel isoquinoline and quinazoline-fused 1,2,3-triazoles in good-to-excellent yields. The methodology mainly features three new C-N bond formations in one convenient manipulation to construct various pentacyclic fused 1,2,3-triazoles, which may possess broad potential applications. Furthermore, the gram-scale reaction, broad substrate scope, excellent functional-group compatibility, and H₂O as the only by-product, further demonstrate the atomic economy of this method.
Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27217567/s1, characterization data, 1H NMR and 13C NMR of compounds 1a–1j, 3aa–3av and 3ba–3ja, and crystallographic data of 3aa. References [81–83] are cited in supplementary materials.

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