2-Alkynylarylnitrile: An Emerging Precursor for the Generation of Carbo- and Heterocycles

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ABSTRACT: In the pursuit of a coherent synthetic route for the synthesis of carbo- and heterocycles, 2-alkynylarylnitrile has been recognized as a useful and versatile building block in organic synthesis due to the dual capacity of this precursor to act with a nucleophilic or electrophilic nature. The alkyne implanted at the ortho position improved the reactivity of the substrate for tandem cyclization and annulations, which led to the synthesis of diverse and complex cyclic compounds. This mini review summarizes the literature on the synthetic transformations of 2-alkynylarylnitrile into biologically relevant heterocycles as well as carbocycles such as isoindoles, isoquinolines, naphthalenes, and indenones as well as building blocks for the synthesis of various natural products. We hope that this concise review will be a promissory entry for future research in this area.

1. INTRODUCTION

The N,O-heterocyclic compounds are privileged architectures among natural products as well as pharmaceutical compounds (Figure 1).1 The topical renaissance and spectacular advance-

In this review, we have highlighted the nucleophile-triggered syntheses of carbo- and heterocycles utilizing 2-alkynylarylnitriles as synthetic precursors and also described various types of mechanistic pathways involved in organic synthesis (Scheme 1): (a) chemoselectivity of CN over alkyne, (b) selectivity of C- or N-centered nucleophilic cyclization over imine, (c) nucleophilic triggered 6-endocyclization of imine, (d) nucleophilic triggered 6-endocyclization of imine via a 5-exo-dig cyclization, (e) radical-cascade cyclization, and (f) miscellaneous reaction. Finally, from beginning to end, this review aims to unveil the most contemporary contributions of 2-alkynylarylnitrile as an important versatile building block in organic synthesis.

2. PROLOGUE OF 2-ALKYNYLARYLNITRILE

Pioneering work using 2-alkynylarylnitrile 1 as a substrate has been reported by Ohshiro and co-workers. They observed different products depending upon reaction conditions. The isoninolin-1-one 2 was formed as a single product, when substrate 1 underwent thermal treatment in the presence of 2 N NaOH/MeOH via a 5-exo-dig cyclization. However, when refluxed in a concentrated alkaline solution, the product furo[3,4-b]pyridine 3 was obtained as a major product along

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Figure 1. N-/O-functionalized privileged aromatic cores.
with a minor product as isoquinolone 4. To reaffirm the intermediate and anionic pathway, the group first hydrolyzed a cyano group of 1 to amide 5 that was further treated with dilute alkaline solution, and they observed the formation of both 2 and 4, while treatment of 5 with NaOEt only afforded a 5-exo-dig product via an anionic pathway (Scheme 2).3

**Scheme 2. Pioneering Work (1990) on 2-Alkynylarynnitrite in Annulation Chemistry**

Later, a BF₃-etherate-catalyzed synthesis of fused isoindolequinazoline 9 from 2-aminobenzyl alcohol 8 was developed by Akula and a co-worker. The reaction was initiated via an acid-mediated nitrile activation that underwent a nucleophilic attack of primary amine to generate species A that further attacked an alkyne or alcohol to lead to the formation of either species B or C, which facilitated the formation of product 9 via a cyclization. The desired product yield was higher when the reaction with (2-aminophenyl)propan-2-ol and (2-aminophenyl)ethanol was performed compared to that of (2-aminophenyl)methanol due to carbocation stability (Scheme 4).5

In 2019, Kumar and co-workers described a Cu (I)-catalyzed synthesis of alkoxy-substituted 3H-pyrrolo[3,4-b] quinoline 12 in good yield from 2-alkynylarynnitrite 10 using the alcohol 11 as a nucleophile via a 5-exo-dig cyclization. CuI has a dual role in the reaction primarily as a Lewis acid as well as a metal attack on the nitrile group of 1 to generate species I, which is followed by a 5-exo-dig cyclization/protonation to deliver the kinetic product E-7, which further converted to the thermodynamic product Z-aminoisoindole 7. A similar reaction was reported by Chen and co-workers for the synthesis of 3-aminoisoindole 7 in good yield using the lanthanum catalyst La[N(SiMe3)2]3. In the reaction, an amine having an electron-donating or -withdrawing group led to E-selectivity, whereas diisopropylamine and benzylamine failed to give the cyclized product (Scheme 3).4

3. **HETEROANNULATION REACTIONS**

3.1. **Synthesis of Isoindoles via 5-exo-dig Cyclization.**

Isoindoles are a prevalent N-heterocyclic scaffold in various natural products and pharmaceutical molecules. Because of their significant application, various synthetic strategies to access isoindole derivatives have been reported in the literature.

In 2010, Xei and co-workers reported a stereospecific synthesis of aminoisoindole derivatives 7 via a titanium-catalyzed reaction of 2-alkynylarynnitrite 1 with various amines in moderate to good yields. The reaction was well-tolerated with various functional groups. However, it fails to deliver the desired product with aromatic amines. The proposed reaction mechanism was initiated via simultaneous activation of the nitrile and alkyne. Further, amine 6 undergoes a nucleophilic attack on the nitrile group of 1 to generate species I, which is followed by a 5-exo-dig cyclization/protonation to deliver the kinetic product E-7, which further converted to the thermodynamic product Z-aminoisoindole 7. A similar reaction was reported by Chen and co-workers for the synthesis of 3-aminoisoindole 7 in good yield using the lanthanum catalyst La[N(SiMe3)2]3. In the reaction, an amine having an electron-donating or -withdrawing group led to E-selectivity, whereas diisopropylamine and benzylamine failed to give the cyclized product (Scheme 3).4

**Scheme 3. Metal-Aided 5-exo-dig Cyclization**

**Scheme 4. BF₃-Etherate-Catalyzed Cyclization**
catalyst. The reaction shows a 100% regioselectivity favoring the formation of the 5-exo-dig cyclized products (Scheme 5). However, other nucleophiles such as amine and thiol rather facilitated the six-membered cyclized product, which is explained later.

3.2. Synthesis of Fused [c]-Pyridine. Wu and co-workers synthesized the tetrazolo[5,1a] isoquinolines 13 when a reaction was performed between 2-alkynylbezonitriles 1 and sodium azide NaN₃ in the presence of a zinc bromide salt under microwave irradiation. In the mechanism, the azide first reacts with an activated nitrile group to generate tetrazoles II that further underwent 6-endo-dig annulation to give the desired products 13 (Scheme 6). In 2010, Li and co-workers demonstrated a Pt-catalyzed C−O and C−N bond-formation protocol using 2-alkynylarylnitrile as a precursor substrate with alcohol (Scheme 7). The reaction was initiated via a nucleophilic attack of alcohol onto the nitrile group and was followed by a 6-endo-dig cyclization to afford the 14 in lower yields. However, when alcohol variation was considered in this reaction a variety of byproducts was observed, specifically, 14a′, 14aa, and 14aa′. Similar observations were earlier suggested by Nishiwaki et al. The formation of 14a′ defines that the nucleophilic attack of alcohol is a foundational step in the reaction. Further improvement in the yield of desired product 14 was obtained after the amount of the catalyst was increased to 20 mol % using ethanol as a nucleophile.

Recently, Liang groups reported a one-pot domino heteroannulation reaction between 2-alkynylbenzonitriles 1 and various 2-iodoaniline derivatives 15 to provide fluorescent benzimidazole fused isoquinolines 16 in good to excellent yields (Scheme 8). The efficacy of this strategy depends on the nitrogen of the aniline moiety, as it undergoes both nucleophilic pounces on nitrile as well as on the alkyne in the cascade reaction.

3.2. Synthesis of Fused [c]-Pyridine. Wu and co-workers synthesized the tetrazolo[5,1a] isoquinolines 13 when a reaction was performed between 2-alkynylbezonitriles 1 and sodium azide NaN₃ in the presence of a zinc bromide salt under microwave irradiation. In the mechanism, the azide first reacts with an activated nitrile group to generate tetrazoles II that further underwent 6-endo-dig annulation to give the desired products 13 (Scheme 6). In 2010, Li and co-workers demonstrated a Pt-catalyzed C−O and C−N bond-formation protocol using 2-alkynylarylnitrile as a precursor substrate with alcohol (Scheme 7). The reaction was initiated via a nucleophilic attack of alcohol onto the nitrile group and was followed by a 6-endo-dig cyclization to afford the 14 in lower yields. However, when alcohol variation was considered in this reaction a variety of byproducts was observed, specifically, 14a′, 14aa, and 14aa′. Similar observations were earlier suggested by Nishiwaki et al. The formation of 14a′ defines that the nucleophilic attack of alcohol is a foundational step in the reaction. Further improvement in the yield of desired product 14 was obtained after the amount of the catalyst was increased to 20 mol % using ethanol as a nucleophile.

Scheme 5. Synthesis of Pyrrolo[3,4-b]quinoline via a 5-exo-dig Cyclization

Scheme 6. Zn-Salt Supported Annulation Followed via Click Reaction

Scheme 7. Alcohol as Nucleophile in 6-endo-dig Cyclization

Scheme 8. Cu/Base Duo in C−N Bond Formation

Scheme 9. Synthesis of N-Heterocycle Derivatives via a 6-endo dig Cyclization
Interestingly, Shults and co-workers described a base-promoted strategy for the synthesis of pyrano-fused amino-naphthyridine 22 in a similar reaction pathway under a metal-free condition. The key features of the reaction are a metal-free, economical approach and further transformation of product 22 into biomolecules by installing a triazole group via a click reaction (Scheme 9c)\(^\text{(11)}\).

### 3.3. Exo Versus Endo Selectivity

To explain how selectivity occurs in the annulation/cyclization reaction of 2-alkynylarylnitrile in terms of endo-dig and exo-dig cyclization, it is important to know the key factors that govern the determination of exo versus endo selectivity. In this context, Wu and co-workers from 1999 to 2002 did extensive work and described the basis of tunability in the cyclization process. The first explanation based on their work was that the R group in the alkynylarylnitrile decides the fate of cyclization; if R is an aryl group, it will promote the 5-exo-dig cyclized product 5b in place of the 6-endo-dig cyclized product 5a. Again, when they performed the reaction of 2-(alkynyl)arylnitrile 1 with an aryl iodide in the presence of Pd-catalyst, the formation of the 5-exo-dig cyclized product, like diarylmethylenedioisooxazoles, occurred due to a steric repulsion between two aryl groups, whereas R as the alkyl group attached to the alkyne of 1 favored the formation of a 6-endo-dig cyclized product such as 3,4-disubstituted isoxazolines, which overcame the steric interaction. They further explored the role of solvent in the reaction toward the selectivity of two isoelectronic intermediates A or B. They observed that the use of a polar aprotic solvent in the reaction favored the formation of 6-endo-dig transition state A due to the stabilization of electron cloud. On the basis of the above observation, they believe that it could be loosely dependent on the property of the metal. Later on in 2016, the Anand group also confirmed the role of metal to control the regioselectivity by an experimental analysis. When the reaction was performed between alkynylarylnitrile 1 and secondary amines in the presence of CuOTf·PhMe catalyst, the reaction led to the formation of the six-membered cyclized product 5d by a 6-endo-dig cyclization. However, the catalyst Zn(OTf)_2 shows an excellent selectivity toward 5-exo-dig cyclization (Scheme 10)\(^\text{(12)}\).

### Scheme 11. Zn Catalyst Promoting Benzannulation

More recently, Verma and co-workers reported a superbase-promoted intramolecular annulation of 2-alkynylarylnitrile 1 with nitromethane 25 for the synthesis of nitrogen-containing derivatives 26 (Scheme 12)\(^\text{(14)}\).

This reaction allowed a carbon-centered chemospecific synthesis of naphthalene through stepwise C–H bond functionalization. The plausible mechanistic pathway indicates that successive nucleophilic addition followed by an intramolecular cycloaromatization furnishes the desired architecture.

### 4. BENZANNULATION REACTIONS

In 2014, the cyclization of α-propargylnbenzonitriles, with preactivated zinc as a catalyst, afforded a precursor for the synthesis of various natural products such as Taiwanin C and Chinensis. Fan et al. and Srinivas et.al. reported a similar reaction for the synthesis of amine-substituted naphthalene 24 through 6-endo-dig cyclization. They examined that the cyclization of a Blaise intermediate I formed by the action of zinc from α-bromo ester 23 and substrate 1 favored the cyclization acting as competent nucleophile; however, only the C-center was involved in cyclization rather than the N-center (Scheme 11)\(^\text{(13)}\).

### 5. RADICAL CASCADE CYCLIZATION

After an extended study of the effect of an anionic nucleophile on 2-alkynylarylnitrile, in 2017, Jiang groups demonstrated a reverse regio- as well as chemoselective addition of an in situ-generated radical species onto the triple bond of 2-alkynylarylnitriles 1 under various metal catalysts. In the reaction, an unexpected product, namely, phosphorus-containing 1-indenones 28, was observed in place of the benzol[b]-phosphole oxides. Many control experiments proved that these reactions proceed through a radical pathway and that water plays an important role in the generation of indenone. Again in 2018, they also explored this chemistry by introducing a sulfur radical to generate indenone under Cu(II) catalysis. Sun and co-workers have provided a similar strategy for the synthesis of product 28 from 1 via the generation of a sulfur radical under Cu(II) catalysis. Later, Liang groups have also reported a strategy for the construction of sulfonated indenones 28 through a radical-cascade reaction between 1 and sodium arylsulfonilates 27 under a metal-free condition. The mechanistic pathway for such a transformation generally initiated via an R_c-centered radical addition (R_c = P, S, and C-centered radical)
and 5-endo/exo-dig cyclization followed by hydrolysis processes resulted in multiple bond formations such as C−Rc, C−C, and C−O bonds (Schemes 13 and 14).15−19

Scheme 13. Indenone Synthesis via Radical-Cascade Reaction

Scheme 14. Plausible Single-Electron Mechanism for Annulation

6. MISCELLANEOUS REACTIONS

Wu and co-workers observed that an alternative chemoselective product like 4,5-disubstituted-2H-1,2,3-triazoles 29 was formed when precursor 1 was irradiated with a microwave under a thermal condition with sodium azide at 140 °C. In the reaction, azide chemoselectively reacted with alkyne over nitrile in absence of ZnBr₂ catalyst (Scheme 15).7

Scheme 15. Click Reaction over endo/exo-dig Cyclization

Kumar and co-workers performed the reaction between substrate 10 with primary amines/thiols as a nucleophile under the Pd-catalyzed protocol. Surprisingly, they observed hydroamination and hydrothiolation as products 31 instead of cyclized products via an addition of a nucleophile to the C−C triple bond of the alkyne rather than the nitrile group that further converted to a cyclized product in the presence of base (Scheme 16).10

Scheme 16. Nucleophile Effect in Hydroamination/Thiolation

Because of the biological importance of halogenated heterocycles, Kumar groups were interested to develop a protocol for the synthesis of chlorinated carbo/heterocycle using 2-alkynylarylnitrile as starting precursor 10. When the reaction was performed between substrate 10 and POCl₃ as the chlorinating reagent under a metal-free condition, 2-chlorovinylquinoline derivatives were afforded as product 32 in good yields (Scheme 17).20

Scheme 17. POCl₃ Promotes Hydrochlorination over Cyclization

In 2014, Srinivas groups have demonstrated a miscellaneous protocol toward the synthesis of disubstituted 2,3-dihydroazanaphthoquinones 33 by the consecutive oxidation of an alkyne and the hydration of a nitrile group of 2-alkynylarylnitrile 1 (Scheme 18).21 The mechanistic pathway was initiated by the coordination of an activated palladium complex with both alkyne and nitrile groups of substrate 1 to generate species I. The triple bond of species I was attacked by another dimethyl sulfoxide (DMSO) molecule to furnish species II, which further converted to species III in the presence of water. The species III will undergo intramolecular cyclization to form the desired product 33. Further generation of azanaphthoquinone was not obtained due to an unsuccessful dehydratation of product 33. An interesting observation was obtained when 2-alkynylthiophenylnitrile was used as a starting substrate under the standard reaction conditions; it afforded an uncyclized product.
product D that confirmed the formation of intermediate I. This result confirmed that the presence of a thiophene core prohibited the hydration of nitrile in compound D, whereas in the case of a quinoline, the nucleus obstructed the alkyne hydration but favored the nitrile hydration followed by a 6-endo-dig cyclization to deliver the product E.

7. CONCLUSION AND OUTLOOK

In conclusion, we have described an outline of the efficacy of 2-alkynylarylnitrile in recent decades as an alternative synthetic precursor for the generation of carbo- and heterocycles. This mini review also summarizes the reaction pathways like 6-endo or exo dig tandem cyclization and annulation that are involved in the regioselective synthesis of privileged heterocycles using 2-alkynylarylnitriles. Moreover, some of the illustrated protocols lead to the development of frameworks that are analogous to natural products as well as the development of a promising biological candidate or a potential biosensor. Furthermore, a brief survey of the synthesis and application of various compounds such as 2H-chromen-2-one, isoquinolines, naphthalenes, quinolones, and indenones was also described. This mini review has opened a new sight for the development of a new reaction toward the synthesis of novel compounds utilizing 2-alkynylarylnitrile as a synthetic building block.

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Notes
The authors declare no competing financial interest.

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