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Mini-Review

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

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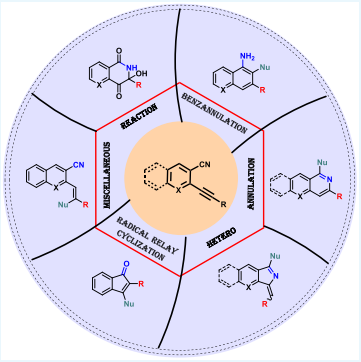
ABSTRACT: In the pursuit of a coherent synthetic route for the synthesis of carbo- and heterocycles, 2-alkynylarylnitrile has been recognized as a useful and versatile building block in organic synthesis due to the dual capacity of this precursor to act with a nucleophilic of electrophilic nature. The alkynes 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 advancement of arylnitrile in organic synthesis is invaluable due to their readily synthetic accessibility and capability to undergo an organic transformation into a range of diverse functional groups like carboxylic acids, amides, amines, aldehydes, ketones, and tetrazoles.[2] 2-Alkynylarylnitrile has emerged as a building block due to the presence of an alkyne group at the *ortho* position of a cyano that enhanced the reactivity of the substrate for tandem cyclization and annulations. The 2-alkynylarylnitriles are most often generated from a Sonogashira coupling of 2-haloaryl nitrile and terminal alkynes using a palladium catalyst. In recent years, this building block has been broadly utilized to access amino-substituted naphthalene, isoquinoline, and isoindoline derivatives along with indenone via a metal or metal-free annulation/cyclization.

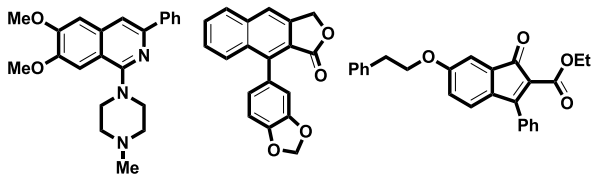


Figure 1. N-/O-functionalized privileged aromatic cores.

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-*endo-dig* cyclization of imine, (d) nucleophilic triggered cyclization 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-alkynylarynitrile **1** as a substrate has been reported by Ohshiro and co-workers. They observed different products depending upon reaction conditions. The isoindolin-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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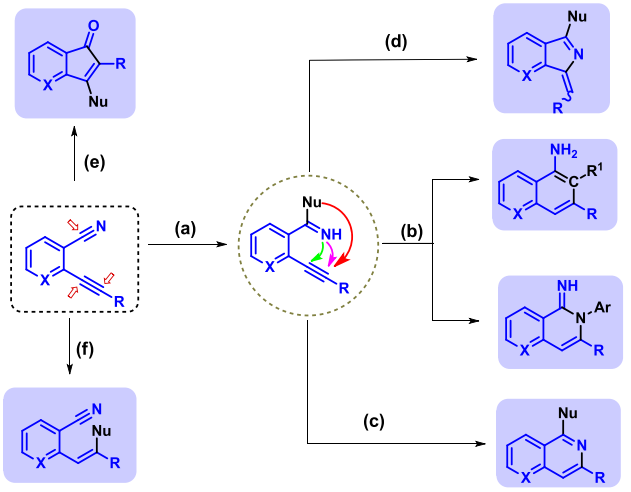
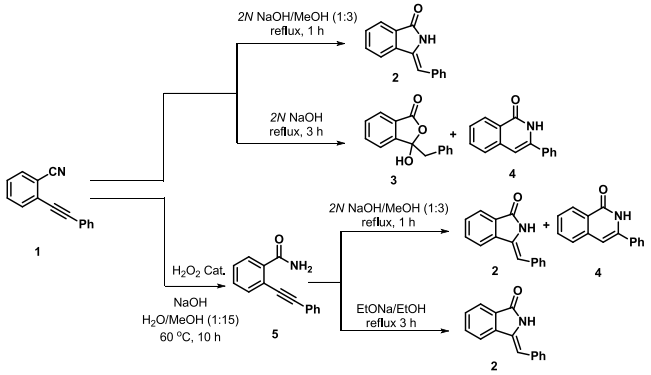
Scheme 1. Five Reaction Pathways[a]



[a](a) Nitrile acting as an electrophile, (b) selectivity of C-or N-centered nucleophilic cyclization over imine, (c) cyclization via a 6-*endo-dig* intermediate, (d) cyclization via a 5-*exo-dig* intermediate, (e) radical-cascade reaction, and (f) miscellaneous reaction.

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-Alkynylarylnitrile in Annulation Chemistry



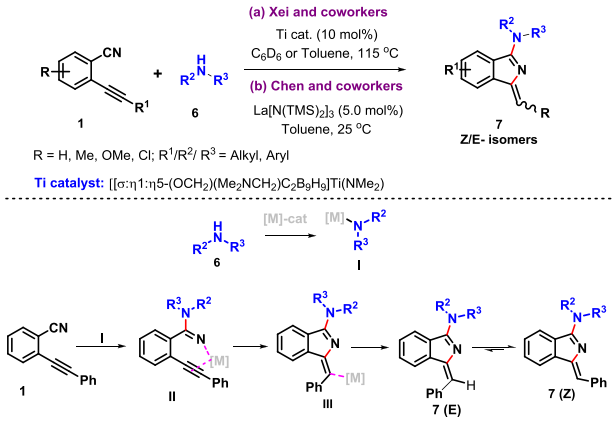
3. HETEROANNULATION REACTIONS

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-alkynylarylnitrile **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 $La[N(SiMe_3)_2]_3$. In the reaction, an amine having an electron-donating or -withdrawing group led to E-selectivity to, whereas diisopropylamine and benzylamine failed to give the cyclized product (Scheme 3).[4]

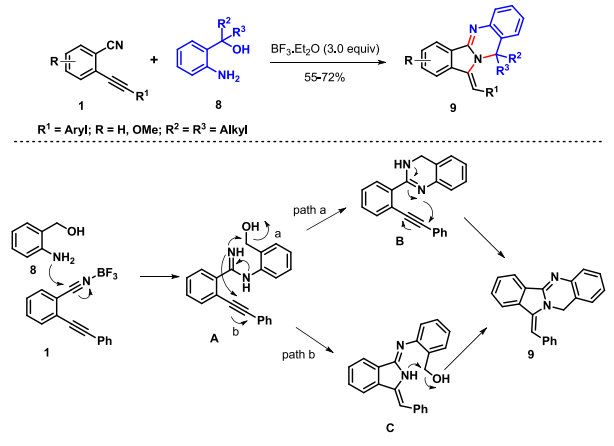
Scheme 3. Metal-Aided 5-*exo-dig* Cyclization



Later, a BF_3-etherate-catalyzed synthesis of fused isoindole-quinazoline **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 3*H*-pyrrolo[3,4-*b*] quinoline **12** in good yield from 2-alkynylarylnitrile **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

Scheme 4. BF_3-Etherate-Catalyzed Cyclization



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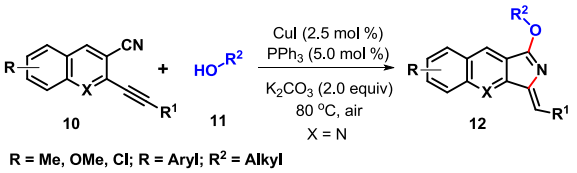
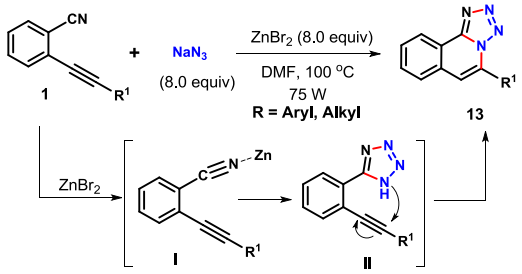
catalyst. The reaction shows a 100% regioselectivity favoring the formation of the 5-*exo-dig* cyclized products (Scheme 5).[6] However, other nucleophiles such as amine and thiol rather facilitated the six-membered cyclized product, which is explained later.

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



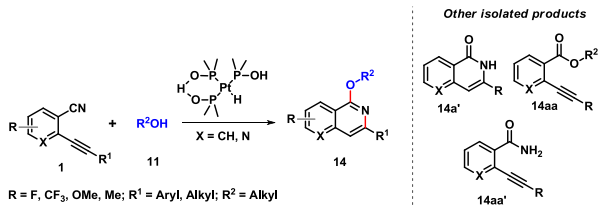
3.2. Synthesis of Fused [*c*]-Pyridine. Wu and co-workers synthesized the tetrazolo[5,1a] isoquinolines **13** when a reaction was performed between 2-alkynylbezonitriles **1** and sodium azide NaN_3 in the presence of a zinc bromide salt under microwave irradiation. In the mechanism, the azide first 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).[7]

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



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).[8]

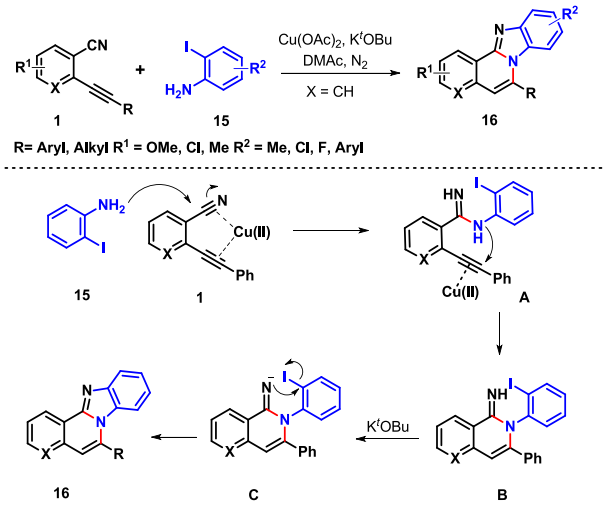
Scheme 7. Alcohol as Nucleophile in 6-*endo-dig* Cyclization



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-alkynylbezonitriles **1** and various 2-iodoaniline derivatives **15** to provide fluorescent benzimidazole fused isoquinolines **16** in good to excellent yields (Scheme 8).[9] The efficacy of this strategy depends on

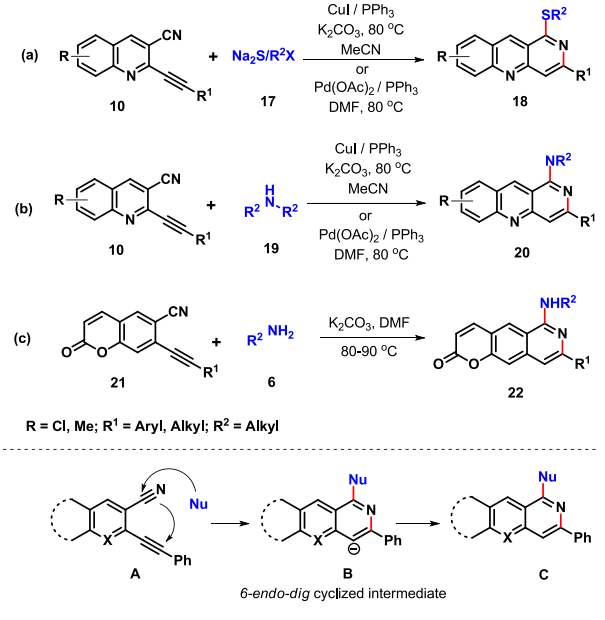
Scheme 8. Cu/Base Duo in C–N Bond Formation



the nitrogen of the aniline moiety, as it undergoes both nucleophilic pounces on nitrile as well as on the alkyne in the cascade reaction.

Again, Kumar et al. explored the Cu-aided protocol for the direct transformation to benzo-naphthyridines **18** and **20** using a secondary amine as well as sulfur nucleophiles through a 6-*endo-dig* pathway, which resulted in lower yields (Scheme 9a,b).[10] In a modified protocol, when a Pd(II) catalyst was used instead of Cu(I) in the reaction, a significant improvement was observed in the yield of polynuclear aza-compounds **18** and **20**.

Scheme 9. Synthesis of N-Heterocycle Derivatives via a 6-*endo dig* Cyclization



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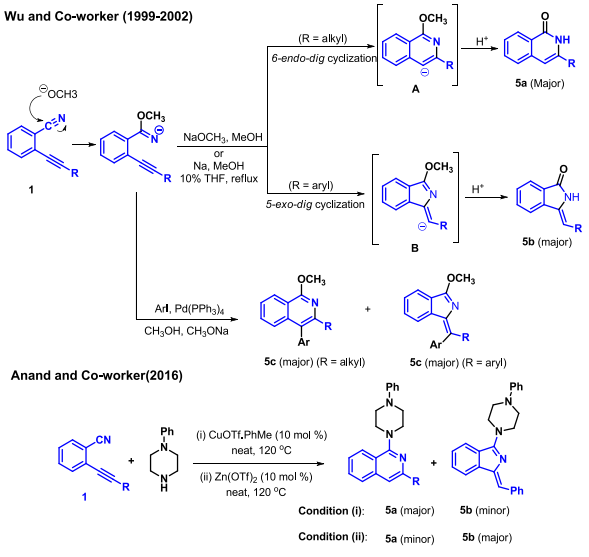
Interestingly, Shults and co-workers described a base-promoted strategy for the synthesis of pyrano-fused amino-naphthyridine **22** in a similar reaction pathway under a metal-free condition. The key features of the reaction are a metal-free, economical approach and further transformation of product **22** into biomolecules by installing a triazole group via a click reaction (Scheme 9 c).[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 diarylmethylideneisoindoles, 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 isoquinolines, 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).[12]

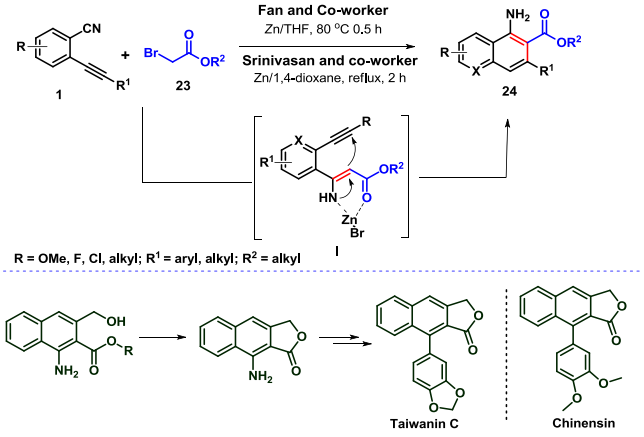
Scheme 10. Effects of Tunable Cyclization



4. BENZANNULATION REACTIONS

In 2014, the cyclization of *o*-propargylbenzonitriles, with preactivated zinc as a catalyst, afforded a precursor for the synthesis of various natural products such as *Taiwanin C* and *Chinensin*. 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).[13]

Scheme 11. Zn Catalyst Promoting Benzannulation



More recently, Verma and co-workers reported a superbase-promoted intermolecular annulation of 2-alkynylarylnitrile **1** with nitromethane **25** for the synthesis of nitronaphthylamines derivatives **26** (Scheme 12).[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.

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 benzo[*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 reported a similar strategy for the synthesis of product **28** from **1** via the generation of a sulfur radical under Cu(I) catalysis. Later, Liang groups have also reported a strategy for the construction of sulfonated indonenones **28** through a radical-cascade reaction between **1** and sodium arylsulfinates **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)

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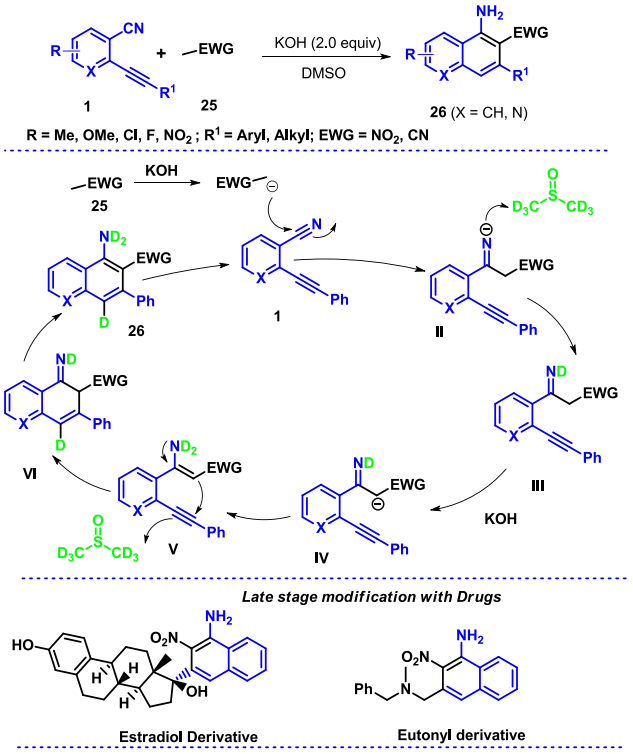
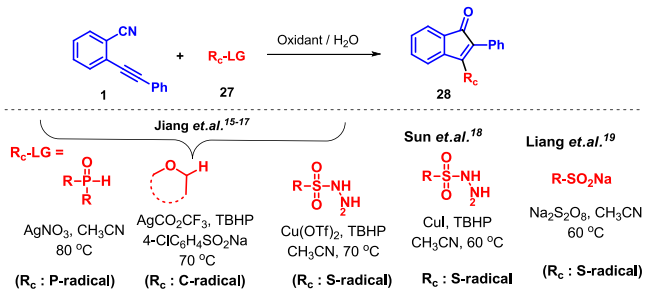
ACS Omega 2020, 5, 32133−32139

Scheme 12. Base-Mediated Benzannulation Reaction

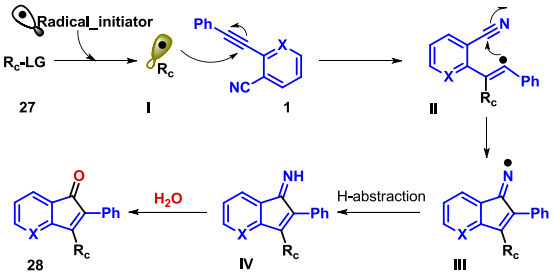


and 5-*exo-dig* cyclization followed by hydrolysis processes resulted in multiple bond formations such as C−R_c, C−C, and C−O bonds (Schemes 13 and 14).[15−19]

Scheme 13. Indenone Synthesis via Radical-Cascade Reaction



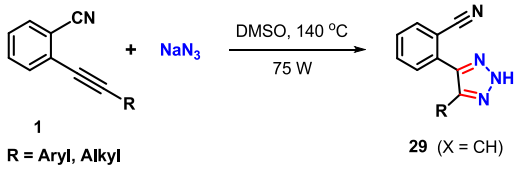
Scheme 14. Plausible Single-Electron Mechanism for Annulation



6. MISCELLANEOUS REACTIONS

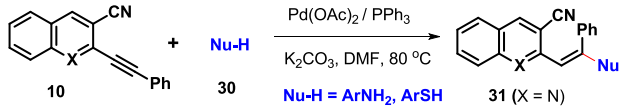
Wu and co-workers observed that an alternative chemosective product like 4,5-disubstituted-2*H*-1,2,3-triazoles **29** was formed when precursor **1** was irradiated with a microwave under a thermal condition with sodium azide at 140 °C. In the reaction, azide chemoselectivily reacted with alkyne over nitrile in absence of $ZnBr_2$ catalyst (Scheme 15).[7]

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



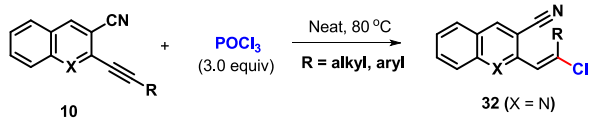
Kumar and co-workers performed the reaction between substrate **10** with primary amines/thiols as a nucleophile under the Pd-catalyzed protocol. Surprisely, they observed hydroamination and hydrothiolation as products **31** instead of cyclized products via an addition of a nucleophile to the C−C triple 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 $POCl_3$ as the choloronating reagent under a metal-free condition, 2-cholorovinylquinoline derivatives were afforded as product **32** in good yields (Scheme 17).[20]

Scheme 17. $POCl_3$ 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 coordintion 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 unsuccesful dehydartion 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

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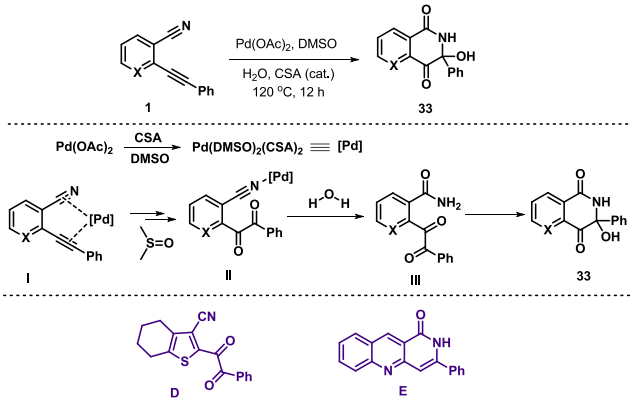
Scheme 18. Hydration-Promoted Synthesis of Azanapthoquinone



product **D** that confirmed the formaion 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 analogues 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 2*H*-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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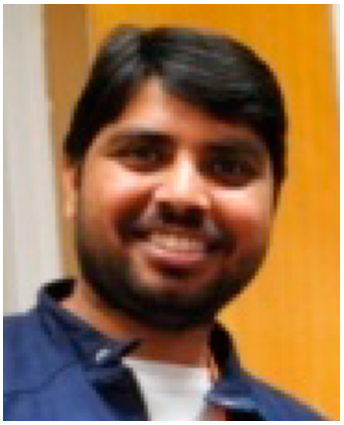
Notes

The authors declare no competing financial interest.

Biographies



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