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ONE-POT REACTIONS INVOLVING ALKYNE ANNULATION: RECENT ADVANCES IN CONSTRUCTION OF POLYCYCLIC NATURAL PRODUCT SCAFFOLDS

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Abstract

In order to synthesize polycyclic scaffolds, the fundamental stages use one-pot techniques called inter- or intramolecular alkyne annulation. These scaffolds are either present in natural products or are associated to them. These methods are either immediately associated with natural products or can be discovered in natural products themselves. We are going to talk about the processes that may be utilized to make particular polycyclic carbocycles and heterocycles that include three or more fused, bridged, or spiro rings. In-depth research will be conducted on the topics of efficient synthetic process and prospective product variety. In this article, we will talk about the many synthetic techniques that may be utilized to synthesis chosen Carbohydrates and heterocycles having at least three ring structures that are fused, bridged, or spiro are considered to be heterocycles. This type of structure is referred to as "at least three fused, bridged, or spiro rings," and substances that have it are called "at least three fused rings." The efficiency as well as the variety of the many different synthetic technologies that are currently accessible will be emphasized. This article focuses on recent applications of recently developed synthetic ideas or toolkits as its primary topic of discussion. C-H functionalization, dearomatization, gold catalysis, collective and divergent total synthesis are all examples of these types of reactions. One-pot cyclization's can be accomplished by the utilization of either multicomponent processes or multifunctional substrates. These reactions are very helpful for the modular and combinatorial synthesis of PNPs as well as the generation of compounds that possess features that are comparable to those of natural products.

Keywords: *One-Pot Reactions, Alkyne Annulation, Natural , Product , Scaffolds.*

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INTRODUCTION

Synthesis of Complex Carbocycles

In 2010, an asymmetric total synthesis of (-)-englerin A was separately reported by both the Ma group and the Echavarren group. Neither group was involved in the discovery of this synthesis. In order to generate oxa-bridged carbocycles in a single step, both groups utilized a technique that was predicated on a cascade reaction that was gold(I) catalyzed. A gold(I)-catalyzed enantioselective cascade cyclization was also reported by the team led by Toste. This process has the potential to be employed in the production of a broad variety of fused scaffolds. These efforts supplied gasoline for gold-catalyzed reactions, which in turn promoted the recent exponential growth as a result of gold catalysis activating alkynes, which then leads to cyclization cascades. In addition, these processes acted as a source of energy that was used in reactions that were catalyzed by gold. [1-4]

In 2014, the group that Echavarren was leading successfully synthesized three natural sesquiterpenes that belonged to the aromadendrane family by using an approach that was both straightforward and asymmetric. A gold(I)-catalyzed cascade cyclization employing a linear dienyne as the substrate was finished in under five minutes when the temperature was kept at room temperature. During this cyclization, the OBn group had a migration of 1,5 positions and underwent an intramolecular cyclopropanetrione. This process involved both cyclopropanation and migration of the OBn group. Three separate procedures are required in order to transform the resultant tricyclic product into either (-)-epiglobulol or (-)-4β,7β-aromadendranediol. It is possible to produce the product that has the opposite configuration by adding an exogenous alcohol, and the product It is possible to get greater selectivity in the reaction by carrying it out at a lower temperature. The stereogenic centers are considered to be a part of this epimeric structure. that are necessary for the synthesis of (-)-4α,7α-aromadendranediol. By following these steps in a single vessel, it is possible to construct three rings with a total of four new stereogenic centers.

The use of alkyne annulations as a synthetic approach for constructing scaffolds from polycyclic natural chemicals is shown here.[5-7]

When compared to fundamental cyclic ring structures, polycyclic scaffolds exhibit a greater degree of structural complexity as well as diversity in their composition. This presents a number of obstacles for synthesis, despite the fact that polycyclic scaffolds are ideally suited for investigating a wider range of the chemical environment. In this study, we examined the changes that have taken place over the course of the preceding ten years in terms of synthetic techniques for polycyclic natural product scaffolds. One-pot reactions that include either

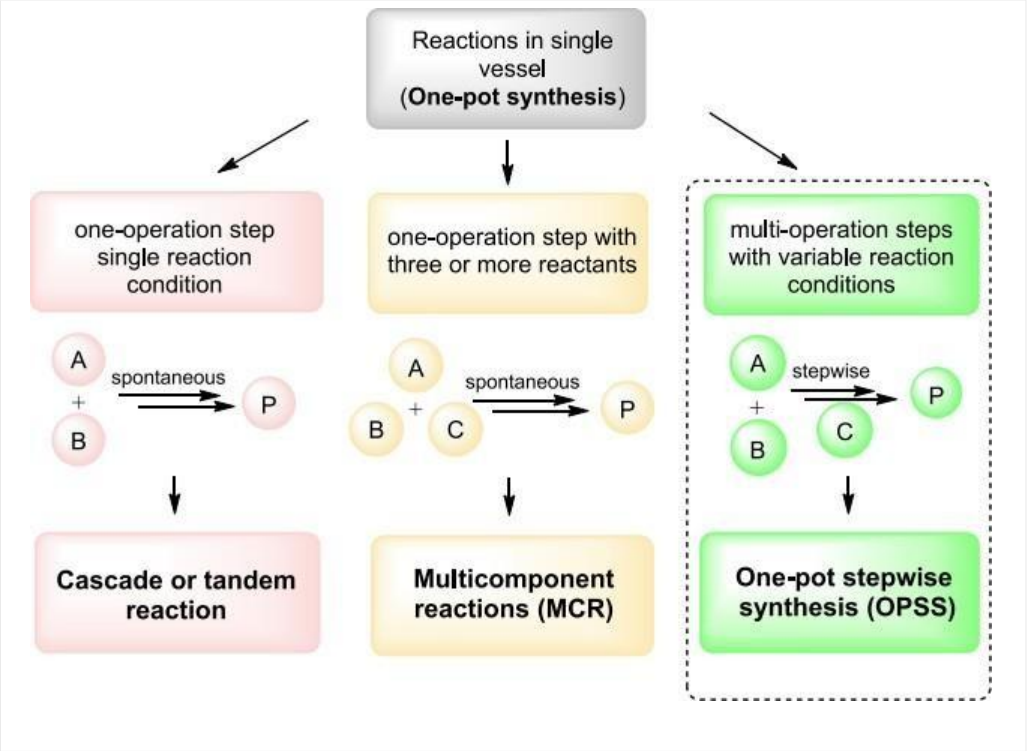
intermolecular or intramolecular alkyne annulation are the key stages in these techniques, and we found that in recent years, they have made a lot of progress. In this article, we will talk about the many synthetic techniques that may be utilized to synthesis chosen Carbohydrates and heterocycles having at least three ring structures that are fused, bridged, or spiro are considered to be heterocycles. This type of structure is referred to as " at least three fused, bridged, or spiro rings, “and substances that have it are called "at least three fused rings." The efficiency as well as the variety of the different synthetic techniques will be emphasized. [8]The purpose of this article is to highlight current instances that make use of freshly discovered synthetic ideas or toolkits. Some of these examples are using a mixture of C-H functionalization, dearomatization, gold catalysis, and full synthesis (in both convergent and divergent forms). In conclusion, a wide variety of various "privileged synthetic strategies" for "privileged polycyclic scaffolds" are

investigated, along with the difficulties those strategies provide and the possible advantages they may bring. Both naturally occurring substances and the synthetic analogues of those molecules can have a wide variety of effects on living things, which renders both classes of molecules vital to the research and development of brand-new pharmaceuticals. On top of that, they are a potent set of tools for researching complex biological systems, such as the ones involved in determining the activities of proteins. This makes them particularly useful in the field of protein function research. Polycyclic natural products (PNPs) are a prominent type of desired structure for the purpose of drug development because of their one-of-a-kind reactions and varied interactions with biological systems, as well as their complicated scaffolds that include functional groups that are placed in an orderly fashion. Among these, polycyclic natural chemicals stand out as possibilities that are very highly wanted. [9-11]

One-pot reactions have distinct procedures

As shown in Scheme 1, each of these three reactions that may be completed in one pot calls for a distinct sequence of steps to be carried out. A series of reactions that takes place in a single step is called a cascade reaction. This sequence of occurrences is referred to as a domino effect or a tandem effect. Once a chemical reaction has begun, none of its components—reactants, reagents, or catalysts—are added any further. in which it is taking place. This ensures that the reaction is carried out exactly as intended. For instance, the cascade radical cyclization technique was utilized in order to effectively synthesis (+/) hirsutene from scratch (Curran and Rakiewicz, 1985). [12-13]A single-operation reaction known as a multi-component reaction (MCR) is characterized by the presence of three or more reactants as opposed to a single reactant. The MCRs Ugi, Biginelli, and Petasis, as well as Gorecki-Blackburn-Bienayme, are

just some of the most well-known examples. Because of its modular design, an OPSS is an excellent choice for the stepwise addition of reactants, reagents, and catalysts to a reaction. It's possible that the circumstances of the reaction will shift between each stage. There are several excellent instances of OPSS, such as the synthesis of particular biomolecules, To produce peptides, a process known as chemical synthesis is carried out with the use of solid-supported reagents and scavengers, polymer synthesis, and so on. Each of these examples is remarkable in its own right. There are a lot of different OPSS that rely on biocatalysis, and you can find descriptions of these systems in the scientific literature. Only the OPSS of physiologically important small heterocyclic compounds found in aqueous solution is the primary focus of this investigation on our part.



Scheme 1. Diagrammatic illustration of three reactions that only require one pot.

OBJECTIVES OF THE STUDY

1. To study on Carbocycles with Polycyclic Rings Built From Scratch

2. To study on Synthetic approaches for constructing scaffolds made ofpolycyclic naturalproducts using alkyne annulations

RESEARCH METHOD

All commercial reagents are already purified to an analytically acceptable level and may be used directly without any further processing. Spectra of nuclear magnetic resonance (NMR) were obtained by employing an ECA-400 spectrometer to collect the data.[14-19] $CDCl_3$ as solvent at 298 K. ^1H NMR (400 MHz) chemical shifts (δ) were referred to the TMS standard

that was used internally. (for 1H, δ = 0.00 ppm). ^{13}C NMR (100 MHz) There was a mention to chemical alterations in the internal solvent. $CDCl_3$ (for ^{13}C, δ = 77.16 ppm). A micrOTOF-Q spectrometer was used to obtain the high-resolution mass spectra (HRMS) using electron spray ionization (ESI). On a GC-MS-QP2010S (Shimadzu, Tokyo, Japan) equipped with a PEG-25M column, the mass spectra (MS) were collected. [20-25]

Procedure that is Typically Followed in the Laboratory for the Synthesis of 3,5-Diphenyl Pyridine (3aa)

A combination of phenylacetylene (1a, 408.1 mg, 4.0 mmol), benzamide (2a, 121.5 mg, 1.0 mmol), and phenylacetylene (1b, 121.5 mg, 1.0 mmol). Cs_2CO_3 (815.1 mg, 2.5 mmol) at room temperature, 4.0 milliliters of sulfolane was swirled in a thick-walled 25 milliliter screw- capped Pyrex tube. 135 °C for 24 h in a tub filled with oil. After allowing the reaction mixture to cool down to room temperature, it was then transferred to a solvent mixture that was made up of water (50.0 mL) and ethyl acetate (25.0 mL), after which the two stages were separated from one another. The aqueous layer was removed using ethyl acetate during the extraction process. (3 × 15.0 mL), an anhydrous medium was then used to dry the mixed organic extracts. Mg_2SO_4. After the solvent was evaporated at a low pressure, the remaining residue was put through a column chromatography process

employing silica gel, petroleum ether, and ethyl acetate to achieve purification (gradient mixture ratio from 100:0 to 90:10) as eluent to afford **3aa** as a white solid (177.9 mg, 77%). (*E*)-1,3-diphenylpropene was isolated in 75% yield.[26-28]

The information that pertains to the structural characterisation of each product in the supplementary materials. An investigation into recent developments made This paper analyzes and demonstrates significant breakthroughs in either the entire synthesis of natural products or synthetic techniques for the manufacture of natural product-like molecules that have occurred over the course of the preceding decade (2010-2020). The primary focus of this research was on recent developments in total synthesis of natural substances or synthetic methodologies, depending on which aspect of synthesis was being examined. The majority of the polycyclic scaffolds that are going to be discussed in this article are going to be the kinds that have at least three rings that are either fused, bridged, or spiro. Despite the fact that scaffolds that are created by the connecting of a large number of simple rings are not only common but also significant,this is the case. When it comes to the synthesis, we would like to place more of a focus on cascade cyclisation's, which include method requiring at least three reactive sites or components, in addition to an alkyne, to be carried out.In addition, we would like to incorporate transformations that make use of a single pot and two stages in the process.[29-34]

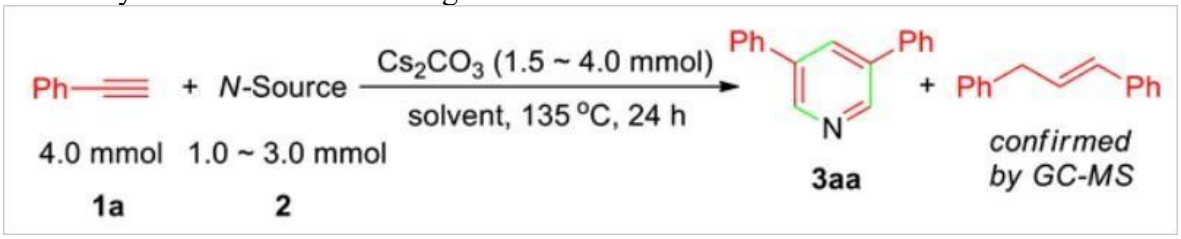
DATA ANALYSIS

In order to begin the process of producing a nitrogen-heterocyclic molecule, we will firstinitiate cyclocondensation of alkyne with benzamide that is catalyzed by a base. After heatinga mixture of phenyl and acetylene (1a, 2.0 mmol), benzamide (2a, 1.0 mmol), and KOtBu (2.0mmol) in DMSO (2.0 mL) at 135 °C for 24 hours, trace amounts of 3,5-diphenylpyridine (3aa)and 1,3-diphenylpropene were produced, as measured by gas chromatography-massspectrometry. During the course of the process, both of these compounds were synthesized concurrently. Because there has never been a report on the synthesis of 3,5-disubstitutedpyridines in a one-pot technique beginning with alkynes, the formation of 3,5-disubstitutedpyridines is of great interest to us. This is because there has never been a report on the synthesisof 3,5-disubstituted pyridines. In addition, alkynes are capable of going through an undiscovered transition that results in 3,5-disubstituted pyridines being produced. [35-38] Because of this, we came to the realization that the reaction conditions needed to be adjustedbefore we could effectively create and provide a synthetic method for getting access to 3,5-disubstituted pyridines by utilizing this innovative form of the alkyne annulation procedure. Asa consequence of this realization, we came to the conclusion that we needed to develop anddeliver an effective synthetic approach. On the basis of the synthesis of 3aa and the structureof the by-product, it is able to confirm that the creation of 3aa requires 4.0 equivalents of 1a inorder to occur, as shown in Scheme 1. Therefore, in order to find the optimal conditions for thereaction, 4.0 mmol of 1a was utilized, and the reactions were carried out under a wide range ofvaried conditions.[39-41]

As can be seen in Table 1, the reactions that took place in DMSO between 1a (4.0 mmol) and benzamide (2a, 2.0 mmol) while also containing 4.0 mmol of 1a are presented. of KO^{t}Bu, KOH, and K_2CO_3 resulted in a trace amount of **3aa** formation, confirmed by GCMS of the reaction mixtures. In the case of Cs_2CO_3 used, delightedly, **3aa** could be isolated from the reaction mixture in 20% yield (the yield was based on the total amount of **1a** used). 3,5-Diphenyl pyridine (3aa) is a

known chemical, the structure of which was validated by its spectroscopic data and x-ray diffraction investigations. The creation of the pyridine ring was unambiguously established by its x-ray diffraction studies. The production of 3aa was reduced to an insignificant amount when In entries 4–8, it is mentioned that different solvents were used. Some examples of these solvents include THF, 1,4-dioxane, DMF, and DMAc (N, N-dimethylacetamide). A dipolar aprotic solvent known as Surfoplane, which is also known as tetramethylene sulfone or 2,3,4,5-tetrahydrothiophen-1,1-dioxide, has a wide variety of applications in both the laboratory and the industrial setting. Both of these words refer to the

same substance that is produced by a chemical reaction. In the process of chemical synthesis, it is frequently employed to bring about significant improvements in reaction rate and selectivity, and it is predicted that this solvent will dissolve alkali metal salts more easily. Because of this, we repeated the reactions in sulfolane several times while employing different concentrations of 2a. As a consequence of this, we were able to successfully create Cs2CO3, the needed 3aa, with yields that ranged from bad to good. [42-43]



The best circumstances for the reaction between 2a (1.0 mmol) and Cs2CO3 (2.5 mmol) resulted in the production of 3aa with a yield of 77% (based on the quantity of 1a that was used in half the reaction). This was one of the reactions. In this specific circumstance, the by-product of 1,3-diphenyl propene was isolated with a yield that was comparable to that of the primary reaction. The yield was 75%, and it was based on using half the quantity of 1a that was originally used. This by-product has a number of potential applications, but in order to obtain it, one would need to apply unconventional approaches to organic synthesis. (Their 1H, 13C NMR spectroscopic data and/or GC-MS), in conjunction with the synthesis of benzoic acid (which was validated by GCMS following work-up by the addition of water; it was not isolated), Repeating the reactions in DMSO, DMF, formamide, and DMAc while utilizing the same amount of Cs2CO3 each time resulted in either a poor yield of 3aa or the absence of any product at all. If step 2a was altered in such a way that NH4OAc or acetamide was utilized as the source of nitrogen, the creation of the product that was anticipated to occur did not take place. It's possible that acetamide's ineffectiveness is due to the fact that it's more basic than benzamide, which is the drug it's supposed to replace. In addition, there was no proof that a product was manufactured in the absence of a base, and this was a significant finding.[44-46]

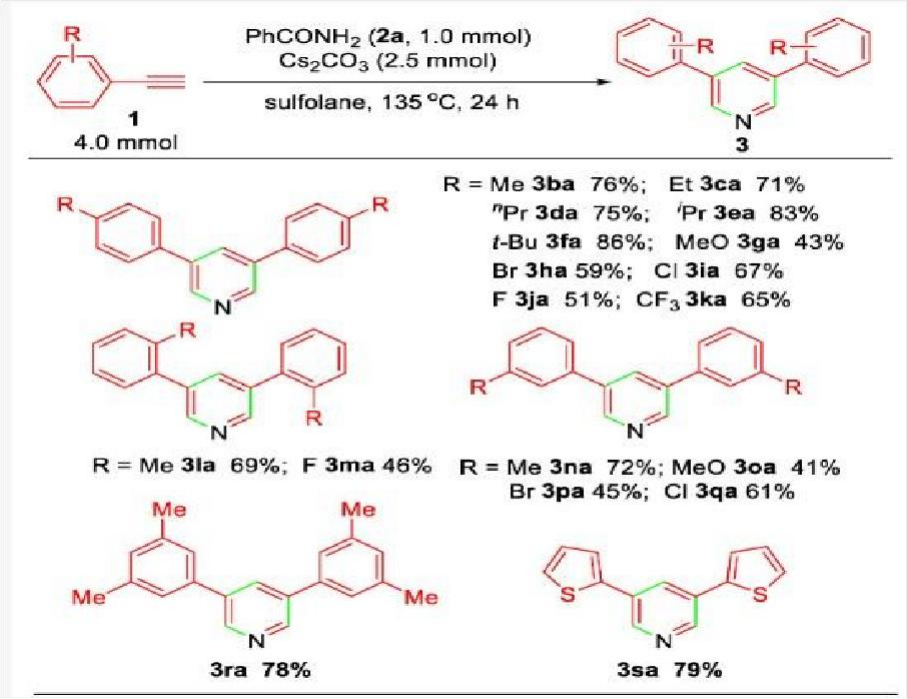
Table 1. Attempts to optimize the reaction conditions for the production of 3,5-diphenylpyridine (3aa) [a].

Scheme 2 Formation of 3aa and the structure of the by-product

Entry	2a (mmol)	Base (mmol)	Solvent	Yield (%)
1	benzamide (1.0)	Cs_2CO_3 (2.5)	formamide	0
2	benzamide (1.0)	Cs_2CO_3 (2.5)	DMAc	25 [c]
3	NH_4OAc (1.0)	Cs_2CO_3 (2.5)	sulfolane	0
4	acetamide (1.0)	Cs_2CO_3 (2.5)	sulfolane	0
5	benzamide (1.0)	--	sulfolane	0
6	benzamide (2.0)	Cs_2CO_3 (4.0)	DMAc	15 [b]
7	benzamide (2.0)	Cs_2CO_3 (4.0)	sulfolane	25 [b]
8	benzamide (3.0)	Cs_2CO_3 (4.0)	sulfolane	16 [b]
9	benzamide (1.0)	Cs_2CO_3 (2.5)	sulfolane	77 [c]
10	benzamide (1.0)	Cs_2CO_3 (1.5)	sulfolane	63 [c]
11	benzamide (1.0)	Cs_2CO_3 (2.5)	DMSO	33 [c]
12	benzamide (1.0)	Cs_2CO_3 (2.5)	DMF	0
13	benzamide (2.0)	KO^{t}Bu (4.0)	DMSO	trace
14	benzamide (2.0)	KOH (4.0)	DMSO	trace
15	benzamide (2.0)	K_2CO_3 (4.0)	DMSO	trace
16	benzamide (2.0)	Cs_2CO_3 (4.0)	DMSO	20 [b]
17	benzamide (2.0)	Cs_2CO_3 (4.0)	THF	0
18	benzamide (2.0)	Cs_2CO_3 (4.0)	dioxane	trace
10	benzamide (2.0)	Cs_2CO_3 (4.0)	DMF	trace

[a] After inserting 4.0 mmol of component 1a, component 2, and base in 4.0 mL of solvent and sealing the tube, the Reactions were carried out when the temperature was at room temperature. The reactions were carried out by placing the tube in a sealed container.135 °C for 24

h. [b] Yields of **3aa** were calculated on basis of the amount of **1a**. [c] The yields of 3aa were calculated based on the quantity of 1a that was divided in half and used as the basis for the calculation. After that, the current alkyne ring closure, which occurs with substrate 2a, which gives rise to 3,5-disubstituted pyridines, was investigated under the circumstances that had been optimized for the reaction (entry 11 of Table 1). According to the findings that are outlined In Scheme 2, aromatic terminal alkynes are depicted. These aromatic terminal The alkyl group in an alkyne is both a donating and a withdrawing substituent. substitutes were identified to be most stable. (Cl, F, CF3) could go through the annulation process in order to produce the appropriate pyridines **3ba~3sa** yields ranging from modest to excellent, although it was found that electronic effects of aromatic terminal alkyne substituents appeared to be dependent on one another. Thus, alkynes **1b~1f**, **1l**, **1n,** and **1r** bearing electron-donating groups (R = Me, Et, ^{n}Pr, ^{i}Pr, and *t*-Bu) when compared to halogen-substituted alkynes, alkynes substituted at the para-, ortho-, or meta-position are more reactive (R = Br, Cl, F, **1h~1k**, **1m**, **1p~1q**).[47]



Scheme 3. Substrate scope of pyridine synthesis.

After inserting component 1 (4.0 mmol), component 2a (1.0 mmol), and component Cs2CO3 (2.5 mmol) in 4.0 mL of sulfolane inside of a sealed tube, the reactions were carried out by heating the mixture for twenty-four hours at 135 degrees Celsius. The amounts of 2a that were used were included into the calculations used to determine the yields.[48]

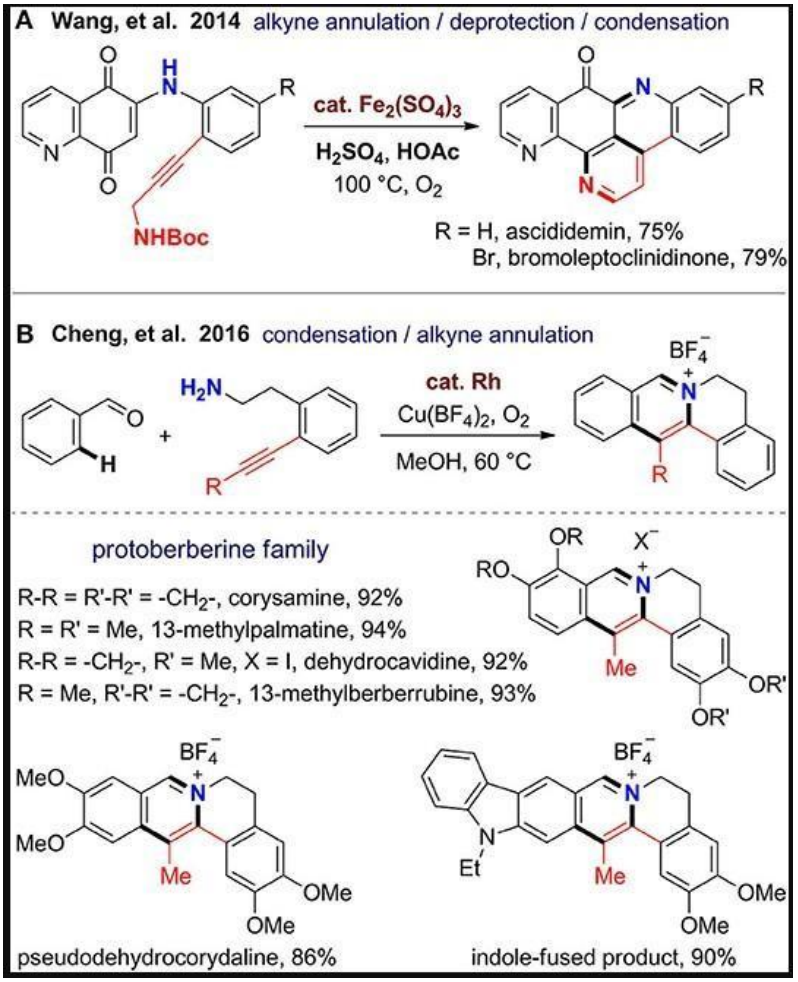
In addition, heteroaromatic terminal alkynes were able to profit from the annulation process that was being carried out. When the reactant 2-ethynylthiophene (1s) is subjected to the regular reaction conditions, for example, 3,5-di(thiophen-2-yl) pyridine (3sa) may be produced with a yield of 79%. This is the case when the reaction is carried out under standard circumstances. It is essential to point out that despite the conditions of the normal reaction, there were two occasions in which the substituent effect could not be identified. This is something that should be taken into consideration. The electron-rich para-methoxy phenylacetylenes (1g) and meta- methoxy phenylacetylenes (1o) both displays comparatively mild reactivity to give rise to the corresponding pyridines, with yields of 43% and 41%, respectively. Because of this, a sizeable quantity of enamine derivatives that were produced as a result of the addition reaction that took place between 1g or 1o and 2a under basic circumstances were found to be present in the reaction mixtures when analysed by GCMS. This was due to the potent electron-donating methoxy group, which prevented the production of amide anion for further transformation (for more details regarding this topic, please refer to the part that is located below this one).

Synthesis of Heterocyclic Compounds Pyrroles and Pyridines Joined Together

Natural products contain a diverse selection of nitrogen-containing aromatic rings (such as pyridine, pyrrole, quinoline, isoquinoline, and indole, for example). Other structures include indole. These nitrogen-containing aromatic rings are also sought after as substructures in a wide

array of PNPs that have substantial pharmacological effects. In 2014, the research team that was directed by Wang announced that they had successfully accomplished a thorough synthesis of ascididemin-type alkaloids. This accomplishment was announced by Wang.

These alkaloidshave an unusual pentacyclic structure that is composed of three pyridine rings in a ring configuration. Using propargylamine-derived quinone substrates makes it possible to carry out an easy Brnsted iron(III) has a mediating role in an oxidative cascade alkyne annulation that takes place under acidic circumstances. Iron(III) is a catalyst that is used in the oxidation process. Full annulation requires a number of different chemical reactions, including C-H functionalization, Boc group deprotection, ketone-amine condensation, and isomerization. Even if two rings will be created in the same vessel, it is possible to improve the overall efficiency of the synthetic process. If the process of producing the substrate by oxidative amination can be incorporated into the phase of annulation, then the reaction can be carried out from fundamental building blocks in an intramolecular form. This is only possible if the phase of annulation can be performed. If this is the case, then the reaction is known as annulation.



Scheme 4. One-pot synthesis of polycyclic natural compounds fused to pyridine.

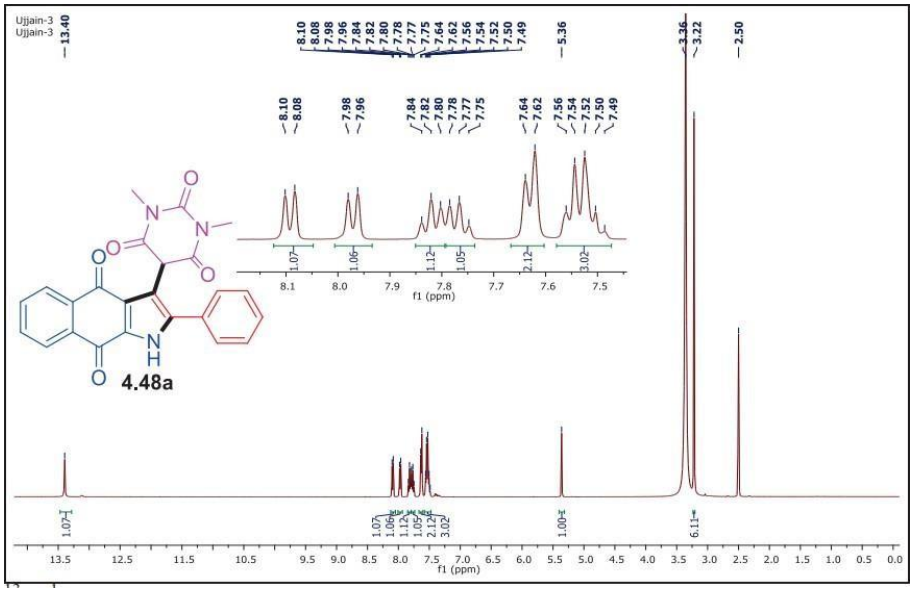


Figure 5 Compound 4.48a's 1H NMR (400 MHz) spectra in DMSO-d6

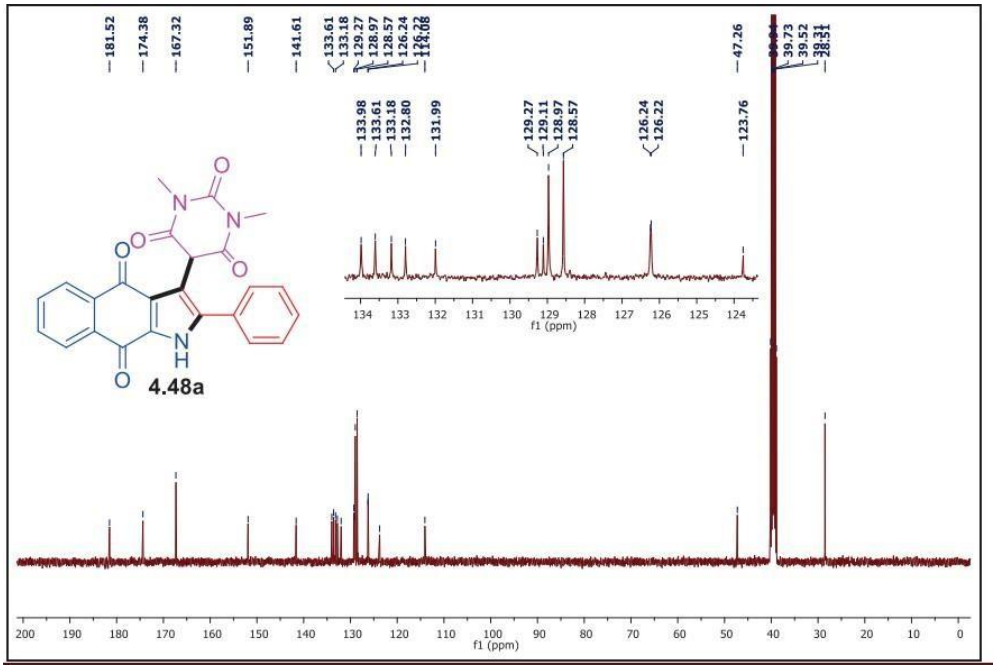


Figure 6 Compound 4.48b's 1H NMR (400 MHz) spectra in DMSO-d6

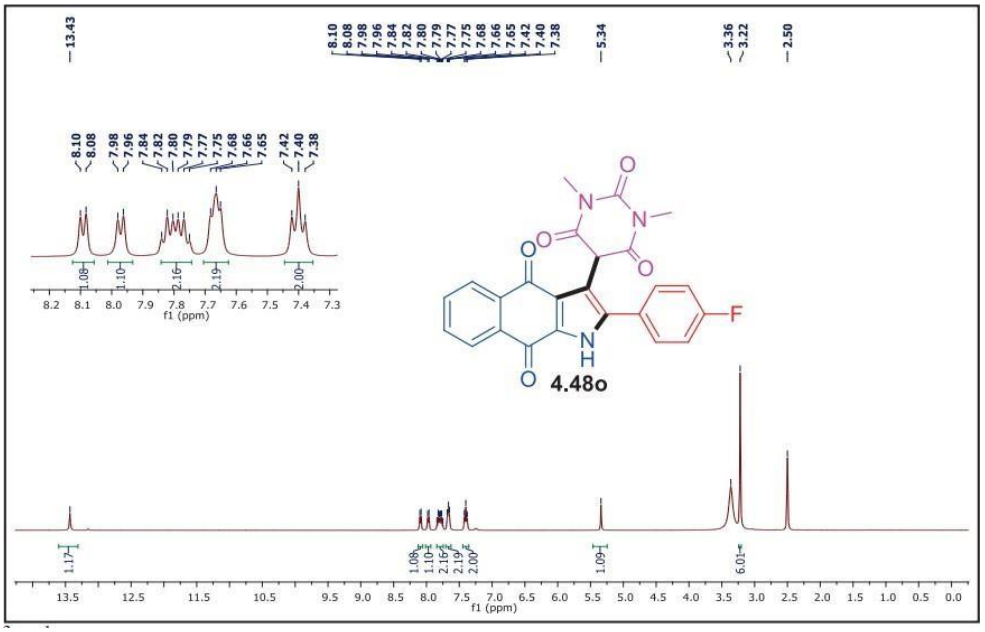


Figure 7 Compound 4.48o's 1H NMR (400 MHz) spectra in DMSO-d6

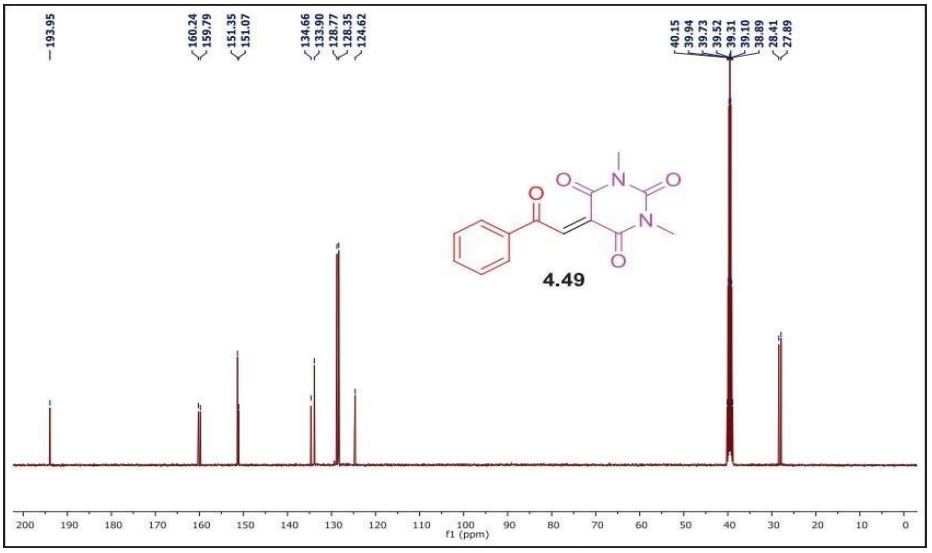


Figure 8 Compound 4.49's 13C- 1H NMR (100 MHz) spectra in DMSO-d6

Two different approaches to the speedy assembly of pyridine-fused heterocycles have been developed by our group. The first technique includes intermolecular or intramolecular alkyne annulation, while the second method utilizes C–H Activation that is supported by the Oxime Automated Directing Group. Both of these methods are described in more detail below. The structure of cassiarins, a family of naturally occurring compounds originating from Cassia siamea and characterized by a tricyclic scaffold, served as an inspiration for both of these approaches. (Scheme 4). In-situ oxime synthesis followed by C–H activation or annulation may be used to create the tricyclic scaffold of cassiarin C. Afterward, DDQ can be used to dehydrogenate this scaffold even more, resulting in the scaffold for cassiarin A. The chroman-

4-ones that are readily available to the researcher are the substrates for this reaction. Strong regioselectivity for

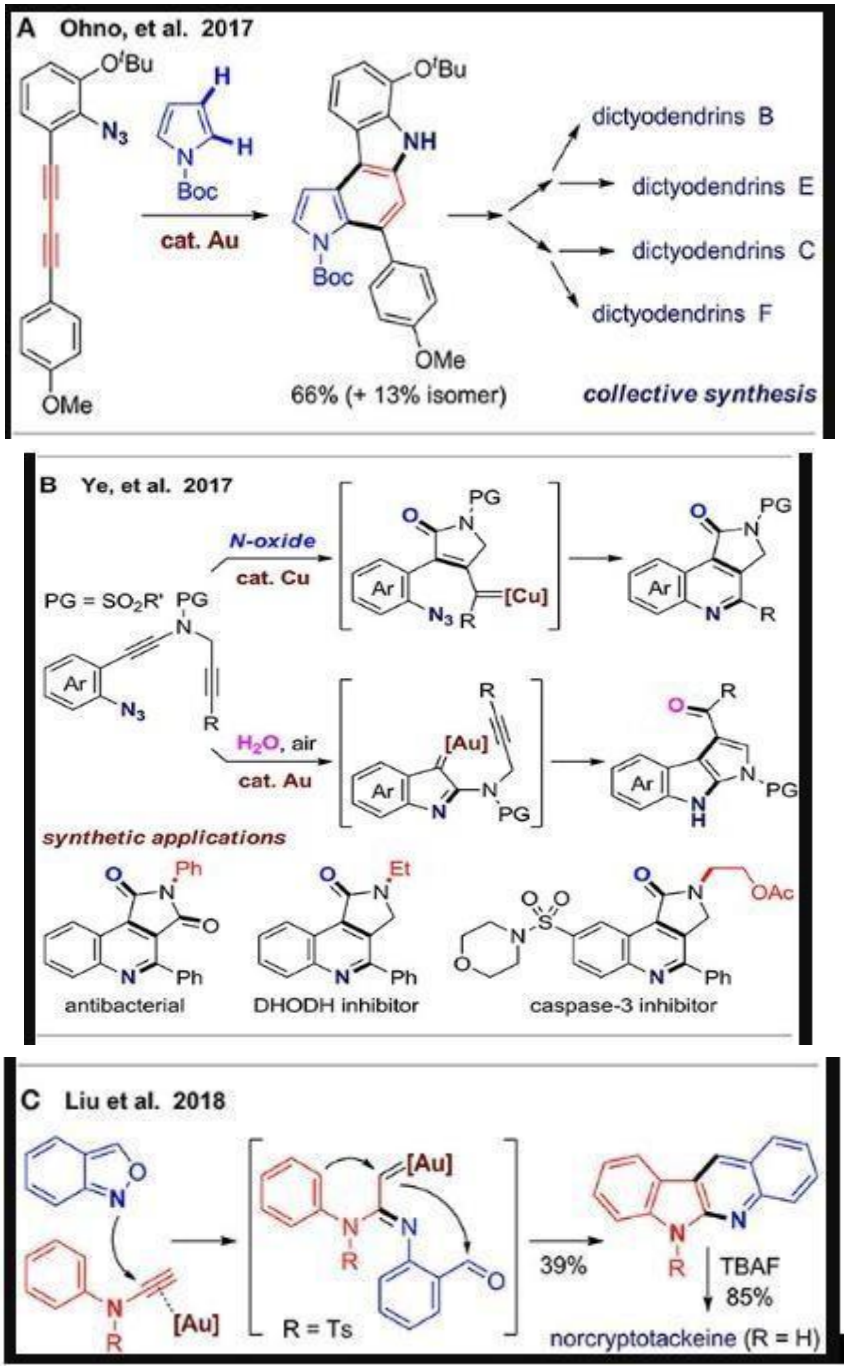
asymmetric alkynes is possessed by the reaction, and it displays high capability of forming stable functional groups when combined with chroman-4-ones.

This includes Tolerance of a free hydroxyl group is something that cassiarins have in common with the presence of this group. Cassiarins are able to be transformed thanks to the reaction, which is an added bonus. When a thiochroman-4-one is present, the formation of synthetic analogs containing sulfur can be accomplished with relative ease, which is another advantage of using this compound. In order to make the most of the intramolecular approach, we came up with many unique alkyne–ketone substrates. In just one simple step, these substrates may be produced utilizing a modular design and fundamental building blocks as their construction components. These bifunctional substrates were able to carry out the reactions as expected, which led to a large array of pyridine-fused polyheterocycles being produced as a result.. Especially, γ-Alkyne-tethered 3-acetyl indoles can be utilized as a step in the creation of carbolines with a ring that is either six or seven members strong, as an intermediate. We were able to produce a small library of polyheterocycles by employing the one-pot processes that were discussed previously. These polyheterocycles have the same structural characteristics as cassiarin, isocyanine, and natural products. As can be seen in this example, the C-H activation and annulation pathway has the capacity to generate structural variety from extremely homogeneous building blocks. Marine sponges were the source of the discovery of the family of polycyclic alkaloids known as dictyodendrins. Because of the considerable biological activity of these alkaloids, researchers were inspired to create innovative synthetic methodologies, and the testing ground for these strategies was provided by these alkaloids. Ohno's team detailed the full and formal synthesis of four different dictyodendrins. The dictyodendrins in question have a pyrrolo[2,3-*c*] carbazole core that is generated by the process of cascade alkyne annulation. The azide group and the alkyne that is close to it undergo an intramolecular denitrogenative cyclization for the first time with the assistance of a cationic gold(I) complex that acts as a catalyst. This step is then followed by an arylation that is accomplished by intermolecular coupling with pyrrole. Finally, an intramolecular hydroarylation of the opposite alkyne is performed in order to complete the production of the tetracyclic scaffold (Figure 9A). During the arylation step, managing the regioselectivity becomes an exceedingly critical problem due to the fact that the C–H bonds at both the C2 and C3 sites are reactive.

To our relief, a substrate containing alkoxyl Substituents that interact favorably and generate a product with improved regioselectivity can help facilitate the divergent synthesis of

dictyodendrin B, C, E, and F. These dictyodendrins are all perfect for the application in question. These several dictyodendrins serve a variety of purposes throughout the body. The pyrrolo[3,2-*c*] Carbazole isomers can be highly useful in diversity-oriented synthesis by realigning the preferred substructures of natural products in order to increase the skeletal diversity. While they can be a nuisance in target-oriented synthesis, they can actually be quite useful in diversity-oriented synthesis. This makes perfect sense, considering that pyrrolo is the [3,2-*c*] carbazole isomers are unwelcome by-products in target-oriented syntheses. This is possible due to the fact that the privileged substructures of natural products can be realigned by the pyrrolo[3,2-*c*] derivatives based on the compound carbazole. The same team ofresearchers has broadened the reach of the method by applying it to a wider variety of materials. To prepare one's benzo supply [c]carbazoles and in Dolo molecules. [2,3-*c*] carbazoles, which have the possibility of

being useful in the manufacture of organic compounds.[49]



Scheme 9. Synthesis of nitrogen-containing polyheterocycles in a single step can be catalysed by either gold or copper.

A new type of azido-diyne substrates was produced by the research team. These substrates make it possible to perform the divergent synthesis of valuable N-heterocycles by utilizing controlled cascade cyclization (Scheme 5). In the beginning, there is an oxidative diyne annulation that takes place. Copper(I) acts as both the catalyst and the N–O bond oxidant for this reaction. The next step is a denitrogenate coupling, which ultimately leads to the production of pyrrole[3,4-*c*] quinolin-1-ones. The heterocyclic compounds that are produced as a result are able to go through additional transformations, which can lead to the production of a wide variety of bioactive molecules, such as molecules that have the

ability to inhibit caspase-3, DHODH, and bacteria. When gold(I) is utilized as the catalyst in this reaction, and when water and air are present in the environment, these substrates travel through a different reaction path than they would otherwise. The final products are compounds that have a pyrrolo[2,3-b] indole scaffold, which is also a key structure in a number of other bioactive chemicals. Developed a gold(I)-catalysed bicyclization of alkynes, which resulted in the formation of a tetracyclic framework that was joined together by indole and isochroman. This tetracyclic framework may then be modified into a wide range of fused or spiro polycyclic scaffolds by additional transformation. This was achieved by the authors by the use of azido- alkyne substrates.[50]

CONCLUSION

As a consequence of the ongoing study, a method for the synthesis of 3,5-diaryl pyridines has been developed that is not only easy to follow but also very efficient. This method comprises the use of benzamides as nitrogen sources and the Cs_2CO_3-promoted annulation of aromatic terminal alkynes in sulfolane. Additionally, this method is accompanied by the synthesis of 1,3-diaryl propene's as a by-product of the process. The production of 3,5-diaryl pyridines with high chemo selectivity in a one-pot manner employing a wide spectrum of easily accessible alkynes in the absence of transition metals is one of the noteworthy advantages of this approach. In addition, benzamides were first used in the synthesis of pyridine as nitrogen sources at the

beginning of the process. Numerous forms of alkyne-anticipated one-pot annotative reactions have emerged, and they have been shown to be effective and adaptive for the rapid production of a diverse skeleton. These reactions have been developed from the large diversity of different synthetic processes that are now available. These procedures have the potential to be candidates for "privileged synthetic strategies" in order to build "privileged polycyclic scaffolds." This is because of the fact that they can manufacture "privileged polycyclic scaffolds." During the creation of polycyclic carbocycles, alkynes and alkenes are commonly utilized combined. In certain cases, tethered or bridged heteroatoms may also be present. At least three of the many different kinds of synthetic procedures may be classified as privileged. This is true across the board. Gold-catalysed enzyme cyclodimerizations, These include, but are not limited to, the domino RCM and the cascade metal-catalyzed cyclization/pericyclic reaction. In order to ease the rapid synthesis of a broad range of polycyclic heterocycles, a number of alkyne-anticipated synthetic procedures have been devised. At least two of these tactics have proven to be flexible enough to adjust to unexpected situations. Construction of fused pyridines and pyrroles via cascade C-H activation/alkyne annulation triggered by a nitrogen-containing group like amino, oxime, or azide, and construction of bridged polyheterocycles via cascade alkyne annulation/C- H insertion triggered by a hydrazone or an azide group are two examples of multifunctional substrates that combine C-H functionalization and alkyne annulation. Cascade dearomatization and cyclization of alkyne-tethered indoles to generate polycyclic indolines is the alternative procedure.

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