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RECENT ADVANCES IN THE APPLICATION OF INDOLES IN MULTICOMPONENT REACTIONS

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ABSTRACT

Indoles are some of the most versatile and common nitrogen-based heterocyclic scaffolds and are frequently used in the synthesis of various organic compounds. Indole based compounds are very important among heterocyclic structures due to their biological and pharmaceutical activities. The last decade, in particular, has witnessed considerable activity towards the synthesis of indole derivatives due to the possibilities for the design of polycyclic structures by the incorporation of multiple fused heterocyclic scaffolds in an attempt to achieve promising new heterocycles with chemical and biomedical relevance. In this study, we provide an overview on recent applications of indole in the multicomponent reactions for the synthesis of various heterocyclic compounds during the period of 2012 to 2017.

1 INTRODUCTION

Heterocyclic compounds are important tools in our daily life having an extensive variety of applications such as sanitizers,1 pharmaceuticals2,3 and antioxidant compounds,4,5 corrosion inhibitors,6,7 dye stuff, 8 copolymers,9,10 and as building blocks in the synthesis of organic compounds and natural products. Multicomponent reactions (MCRs) have been extensively used for the synthesis of heterocyclic compounds.11–13 MCRs represent a great tool in organic synthesis for the construction of variety-oriented series of building blocks with potentially interesting biological activities.14–17 The attractiveness of the MCR approach is its easy operation, high selectivity and yield by using minimum synthetic requirements. Indole scaffolds have been

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known for their value in the development of new compounds of pharmaceutical interest.18–20 Up to date, several review articles have been published based on the reactions of indole. Herein, in continuation of our studies towards the synthesis of heterocyclic compounds and multicomponent reactions,23–32 and since there is a wide range of reactions that include indole in the preparation of heterocyclic compounds, this review presents the recent applications of indole in the synthesis of diverse heterocyclic compounds during the period from 2012 to 2017. This review rst discusses indoles' C-3 carbon atom reactivity applicable to electrophilic reactions, followed by MCRs in which the N position of indole is reacted as a nucleophile to afford N-substituted indole products.

2 LITREATURE SURVEY

Unless otherwise noted, 5a (1.5 mmol, 176 mg) in 2 mL of solvent at room temperature was used in all processes. Column chromatography was used to purify the products, and the yields listed are for the isolated compounds. [b] Cyclohexanone (10 mol%) was used. Benzoic acid is known as BA. [d] The reaction was conducted in an oil bath at 80 ºC. After determining the ideal reaction conditions, we looked into the range of substrates. Scheme 2.5 summarises the optimised conditions for the reaction involving a range of indoles. We are happy that several replacements at the indole's nitrogen atom and on its aromatic ring were all consistent with the reaction. We found that the reaction either yielded no yield at all or a decreased yield when the indole nucleus included electron-withdrawing compounds. For instance, the former produced 17% when 5-nitroindole or 7-azaindole were treated under the ideal reaction conditions.

The following at room temperature: indoles (1.5 mmol), I2 (10 mol%, 38 mg), cyclohexanone (10 mol%, 15 mg), and TBHP (70% in H2O, 0.7 equiv., 135 mg). Yields are for the isolated products, which were purified by column chromatography using silica gel (100–200 mesh). yield (6d, Scheme 2.5), although no response was actually seen for the latter. Instead, we got the dimeric product 7 (Scheme 2.5) when 2-methyl indoles were treated under the ideal

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reaction conditions. 2-phenylindole, however, had no reaction. The big phenyl ring's steric repulsion is most likely the cause. Both single crystal X-ray crystallography and NMR spectroscopy were used to characterise every product.

We carried out our sample reaction at the ideal reaction conditions, with radical scavengers such BHT and TEMPO (1.5 equiv. each) present in order to investigate the reaction process. The reaction was mostly stopped by these two reagents. Only 7% of 6a was created by the reaction in the presence of BHT, while 11% of the product was produced by TEMPO. This data suggested a mechanism involving free radicals. There was no discernible drop in yield when the reaction was conducted in the N2 environment, with absolute exclusion of aerial oxygen. This suggests that the product's carbonyl oxygen atom is not derived from the aerial oxygen.

We conducted a blank experiment using 0.5 mmol of cyclohexanone, 0.1 mmol of I2, and 1 mmol of TBHP at ambient temperature. After stirring for 5 hours, we collected an IR spectra to determine the involvement of cyclohexanone. The spectra showed that the OH vibration of TBHP and the C=O vibration of cyclohexanone were absent from the spectrum. This suggests that throughout the reaction, TBHP linked itself to cyclohexanone. When cyclohexanone and hydroperoxide combine, new peroxide is created. This peroxide then experiences a faster homolytic O-O bond cleavage into free radicals than the previous peroxide did. This idea is further supported by the fact that, when DTBP was employed in lieu of TBHP, no response was seen. Thus, based on our control tests and pertinent data, a preliminary mechanism is suggested (Scheme 2.6). When indole and I2 combine, 2-indolyl-3-iodoindoline [A] is created, which then aromatizes to [B]. After another reaction between the intermediate [B] and I2, quaternary carbon cenered 3-iodoindoline [C] is produced. The C-I bond cleaves homolytically in the presence of an oxy radical [E] to produce [F], which then breaks down to produce the end product 6a. The cyclohexanone molecule that was removed was now prepared for a new catalytic cycle. Since the process is yet unclear, further mechanistic research

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is needed. This research is now underway in our laboratory, and findings will be shared soon.

Since indole derivatives are among the most promising structures that are often used in medicines, this moiety is intriguing because it has the potential to usher in a new era in the study of drug development. The synthesis of novel indole derivatives has been a hot issue for companies due to its important applicability in various industrial and medical sectors. Due to its ability to bind with a wide range of biological targets, indole derivatives are mostly found in naturally occurring compounds that are biologically active. Compared to the well-known β-carbolines, research on α-carbolines is trailing behind. The fused indole alkaloids belong to the class of α-carbolines. Only a small number of well-known α-carboline alkaloids have been isolated so far. Derivatives of α-carbolines, such grossularine-1 8a and grossularine-2 8b, have anti-cytotoxic properties. Two α-carboline compounds have been isolated from tunicate Dendrodoa grossularia. Compound 9 is a GABA modulator that is used to anxiety disorders. Mescengricin 10, a naturally occurring α-carboline, is extracted from Streptomyces griseoflavus and employed as an inhibitor of L-glutamate excitotoxicity in neurons. Having been isolated from Cryptolepissanguinolenta, 173 Cryptotackieine 11 has potent antiplasmodial action.

Chemists nowadays find it tough and fascinating to study strategies for improving nucleophilic reactions at the indole ring's C2 and C3 positions. Indoles possess a high electron density and, when it comes to electrophilic substitution, the C3 position is often more active than the C2 position. 175 Nevertheless, under typical circumstances, nucleophilic substitution events in indole are rare. The positions C2 and C3 in indoles often result in electrophilic reactions. Because of this, many significant indole derivatives are difficult to synthesise using the usual reactivity of indole. To get around this restriction, use the polarity inversion technique known as umpolung.

For this reason, modern chemists find the development of the umpolung approach in indoles to be a difficult and

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hard subject. The indole ring, particularly C2 and C3, reacts as an electrophile in this method. The pyrrole ring of indole may have an electron-withdrawing group (EWG) placed on it; an LG can be left at the N1 position in conjunction with an EWG; or an EWG can be placed via metal carbene intermediates. In indole, they are referred to as direct ways for umpolung. Another popular strategy starts with a highly electrophilic iminium intermediate via a conventional electrophilic assault at the C3 site. A nucleophile may then readily attack this intermediate, blocking or promoting the ultimate rearomatization, which is solely dependent on the electrophile's leaving capability. An indirect method of umpolung in indole is this.

According to equation 1, Scheme 2.7, Batey and colleagues have developed a method for the allylation and crotylation reactions of indoles at the C2-position by using allylic trifluoroborate salts through electrophilic addition reaction. Recently, chemists have developed new methodologies to synthesise an important class of indole derivatives by transforming the nucleophilic centre of indole to an electrophilic one. 176a Nishina et al. described the use of BF3·OEt2 in (CF3)2CHOH (equation 2, Scheme 2.7) to achieve C2 site-selective intermolecular nucleophilic addition of an electron-rich aromatic molecule.

Complex molecular structures have been constructed in recent years using a variety of techniques for the creation of the C-O,177, C-N 178, and C-S 179 bonds at the C2 position of the indole ring. Additionally, we intended to use intramolecular cyclization to alter the polarity of indole at the C2 site. Some publications have shown that this mechanism may produce intermolecular C-N bonds in the indole C2 carbon.178 However, there are fewer reports of intramolecular C-N bond production at the indole C2 location. Using Pd(II) as a catalyst and a stoichiometric quantity of silver salt as an oxidant, Yao et al. recently reported the production of a C-N bond at the C2 position of indole, leading to the synthesis of indolo [1,2-a]quinazolinones (Scheme 2.8). The first stage involves the Ullman coupling reaction between 2-iodobenzamide derivatives and indoles. Palladium catalyst is used in the second stage to facilitate intramolecular C–H amidation..

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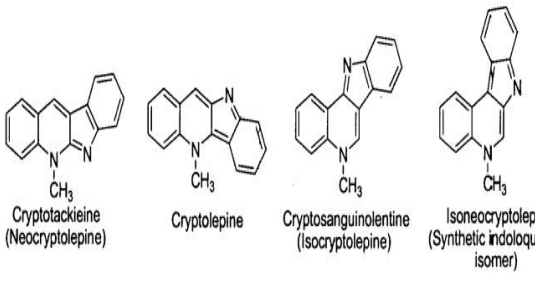
3 METHODOLOGY

The three main synthetic tools that we have developed for the synthesis of indoloquinoline alkaloids are presented in this chapter.

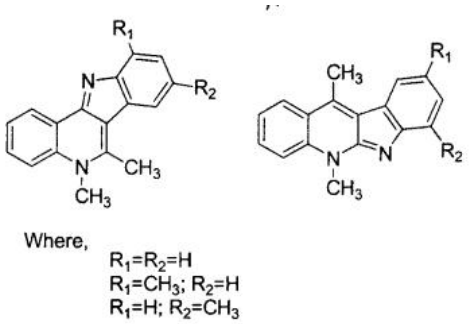
a) Synthesis of Fischer-indole

b) Photoannulation guided by hetero atoms

c) Bucherer synthesis Due to the literature's extensive discussion of the medical significance of indolo quinoline alkaloids, syntheses of these compounds have gained significant attention in recent years. The following indolo quinoline alkaloids and their derivatives have been successfully synthesised by using the aforementioned synthetic techniques. We hope that these methods provide yet another feasible path and are more effective than the previously documented processes.



Methyl derivatives of crytosanguinotentine and cryptotackieine



Using a selective indolization procedure, we have developed and refined dependable divergent methods for the synthesis of target alkaloids from appropriate starting substrates such as hydroxyquinolines or haloquinolines. Fischer and Jourdan published a paper in 1883 on the first arylhydrazone indolization. The Fischer-indole synthesis was discovered more than a century ago, and it is still the most widely used technique for indole production. Even though the synthesis calls for the cyclization of an arylhydrazone, the indole nucleus is often obtained by immediately exposing an equimolar combination of the arylhydrazine and aldehyde or ketone to the indolization conditions, without isolating the hydrazone. The imine nitrogen is first protonated and then

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tautomerized to generate an intermediate ene-hydrazine, usually in an acidic environment. An intermediate is produced by a [3,3] sigmatropic rearrangement that takes place after tautomerization. The 5-membered ring is then formed by cyclization of the imine, which is created by rearomatization via a proton shift. Ultimately, the indole nucleus is produced by the loss of ammonia. Fischer indole synthesis may also be used to synthesise carbazoles and indolo quinolines. It is widely used to synthesise indole and its derivatives, as well as its alkaloids. This article describes a novel synthesis of the indoloquinoline alkaloid crypto sanguinolentine, which is based on a modified Fischer-indole cyclization. By reducing with palladium-carbon, the intermediate 113 is immediately transformed into the desired alkaloid 70 after being transformed by POCI3 into its chloro derivative 114.

In a single step, 4-hydroxy-l-methylquinolin-2(l//)-one 21b reacted with phenylhydrazine hydrochloride using a combination of glacial acetic acid and concentrated hydrochloric acid in the ratio 4:1 (as reported by Kent 96). This produced the indolo quinoline moiety 113 (Scheme-3.1). There are several pertinent reports on this conversion 97'99. Using basic and acidic conditions, Bucherer 100 originally demonstrated this transition in the synthesis of 1-naphthol and phenyl hydrazine. Mulwad et al. recently reported on the transformation of 4-hydroxyquinolin2(l//)-one into derivatives of 4-hydrazinoquinolin-2-one. Here, the IR spectrum confirms that the production of hydrazone is regiospecific at quinoline exposition. 46] of product 113, which demonstrated compound 21b's C4-OH band's absence (3000–3300 cm '). The electronegative nitrogen linked to the C2-carbon shortens the N-C=0 bond length and raises the electron density on the C2-carbon, making it less vulnerable to nucleophilic attack than the C4-carbon. Its "H-NMR spectrum, a multiplet found between 8 7.22 and 8.03 indicates 8 protons, which are the aromatic protons of quinoline and indole.

4 RESULTS

However, upon methylation, the angularly fused system 83 (51%) produced the synthetic indolo quinoline

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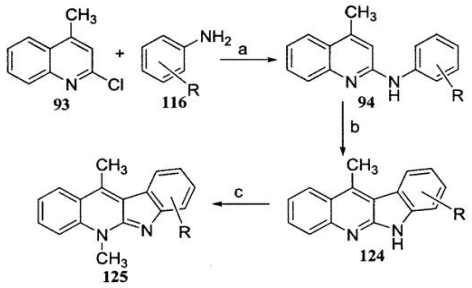
isomer, isoneocryptolepine (122).36 The pathway we selected for the development of the indolo[3,2-Z>]quinoline (quindoline) system and the isomeric indolo [2,3-c]quinoline framework was predicated on their accessibility from a shared intermediate. These structures were previously described by Hostyn et al. at 6, 84 (quindoline alkaloid) and are spectroscopically similar with our synthesised compounds, despite the fact that one dimensional NMR is not useful in differentiating between these isomers. By looking at their corresponding methyl derivatives as well, it was further validated. The synthetic sequence is established when the findings agree with the data from the literature. The spectral and analytical data for 121b. The compounds 84&12329a'ep, 70296'0, 83&12236, and 5629d were spectroscopically similar to the natural products ('H-NMR, °C-NMR). The indoloquinoline alkaloid known as "crypto lepine" was extracted from the root extracts of the African plants Cryptolepis triangularis N.E. Mr. Additionally, C. Aslepiadaceae species sanguinolenta (Lindl) Schlecter is said to have notable hypertensive characteristics.

It's interesting to note that this molecule was created around 20 years before to the alkaloid's first isolation.



Where
116b) R = H, 116e)R = *o*-Me, 116f) R = *p*-Me,
a) Dry ethanol, reflux, 12h; b) hv, C_6H_6:CH_3OH: H_2SO_4, (60:30:0.5), I_2, rt ;
c) Me_2SO_4, toluene, reflux, 6 h, K_2CO_3, 81-82%

As we discussed in the introductory chapter, it has been reported that eryptotackieine, cryptosanguinolentine, and some methyl derivatives (for example, 11-methylcryptotackieine) display various biological properties such as antimuscarinic, antibacterial, antiviral, antimicotic, and cytotoxic activities in vitro. We decided to develop an efficient synthetic route to eryptotackieine and cryptosanguinolentine derivatives in order to study their antiplasmodial activity and cytotoxicity and compare them with the three naturally occurring ones. The synthesis of the more recent methyl derivatives of the same alkaloids is covered in this article. Two methyl-4-hydroxyquinoline and four methyl-2-hydroxyquinoline were used to make them. Both produced the equivalent

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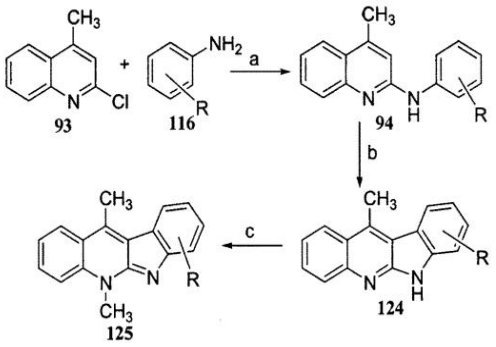
chloro compounds when treated with POCI3. The newer derivatives of indoloquinolines were produced by these compounds by a reaction with aniline and its methyl derivatives, photochemical cyclization, and regioselective methylation.

4.2 5-methyI-5//-indoIo[3,2-c]quinolin -6-o synthesis

Glacial acetic acid, cone, and 4-hydroxy-JV-methyl-quinolin2(l//)-one and phenylhydrazine hydrochloride were added to an equimolar (10 mmol) mixture. After adding HC1 (4:1), the mixture was refluxed in an oil bath with the temperature maintained at 135 °C for almost five hours. Subsequently, the blend was transferred into 300 grammes of crushed ice and refined by silica gel column chromatography employing PE: EtOAc in a 65:35 ratio.

After being introduced to the ice-cold POCI3 solution, the molecule 5-methyl-5//-indolo [3,2-c]quinolin-6-ol was swirled for about two hours. The mixture was then heated for almost three hours at 100 °C. Subsequently, the blend was transferred into 300 g of crushed ice and refined using silica gel column chromatography. PE:EtOAc was used in an elution ratio of 98:2 to get the pure product.



Where
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a) Dry ethanol, reflux, 12h; b) hv, C_6H_6:CH_3OH: H_2SO_4, (60:30:0.5), I_2, rt ;
c) Me_2SO_4, toluene, reflux, 6 h, K_2CO_3, 81-82%

4-Hydroxy-1-methyl-1*H*-quinolin-2-one	1.75 g (10mmol)
Phenylhydrazine hydrochloride	1.43 g (10mmol)
Gla.acetic acid : Concd.HCl (4:1) mixture	50 mL
Yield	1.61 g (65%)
mp	217 °C

Pd-C (10%, 50 mg) was added to a solution of 114 (2 mmol) in 50 mL of ethanol, and the mixture was agitated with H2 at 50 psi in a Parr hydrogenator for 3.5 hours. Alteration was used to remove the catalyst, and ethanol removal under low pressure concentrated the filterate. Following ethylacetate extraction of the residue, the mixed organic layers were dried over anhydrous sodium sulphate and subjected to silica gel column chromatography, which produced a fair

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yield of the angularly fused indoloquinoline alkaloid.

5 CONCLUSION

Vicinal diamines are present in an enormous variety of physiologically important molecules as primary structural components. In addition to being found in a broad range of medicines and natural products, the vicinal diamino functionalities are widely used as a crucial building block in the synthesis of several heterocycles (such as imidazolines and imidazolinones) that have notable bioactivity profiles. Furthermore, because chiral 1,2-diamines are widely found in both transition metal complexes and organ catalysts, they are extremely important in asymmetric catalysis. Among the different chiral vicinal diamines, the one with an unsubstituted CH2 unit and a tetrasubstituted stereo centre (N−CH2−CR2−N) has been identified as a privileged motif in the structure of a large family of heterocyclic compounds with a variety of biological activities, including antitumor, anti-inflammatory, and cardiovascular agents.2 More importantly, the tetrasubstituted homochiral centres of these compounds are crucial to their biological actions. Due to the enantiopure synthesis of these structural components, their widespread distribution has received substantial acknowledgment.

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