Introduction

- **Heteroarylcarbazoles**

Heteroarylcarbazoles are molecules with a heterocyclic moiety fused with carbazole skeleton. The rapidly growing class of heteroaryl-condensed carbazoles began to attract increasing synthetic interest because of their broad spectrum of useful biological activities. To provide an overview on the heteroaryl-annulated carbazole derivatives, these compounds are classified into \[a\]-annulated, \[b\]-annulated, and \[c\]-annulated pyrido-, pyrano-, furo-, pyrrolo-, thienocarbazoles *etc*. This classification is solely based on the position at which the heteroaromatic ring is fused to the carbazole nucleus, either at bond \(a\), \(b\), or \(c\) (Figure 1). In Figure 1, only the structures with a \([4,3]\)-annulated pyridine ring, \([3,2]\)-annulated pyrano- and furan rings are shown, as these are more commonly existing in nature. Moreover, the mode of fusion of the annulated heteroaromatic ring itself can vary, which leads to an even broader variety of heterocyclic ring systems.

**Figure 1**
It is well established that the pyridocarbazole ring system is one of the appropriate skeletons to design DNA intercalating drugs.\(^2\) For this reason, there has been a strong synthetic activity in this area. Examples of potential annulation modes are the pyrido[4,3-a]carbazoles \(1\), the pyrido[4,3-b]carbazoles \(2\) and the pyrido[4,3-c]carbazoles \(3\).

- **Pyrido[4,3-b]carbazoles**

Among the different isomeric pyridocarbazole frameworks, the pyrido[4,3-b]carbazole \(2\) has attracted most of the interest because ellipticine and its 9-hydroxy and 9-methoxy derivatives show significant anticancer activity.\(^3\) In 1959, Goodwin *et al.* isolated ellipticine \(20\), a pyrido[4,3-b]carbazole, from the leaves of *Ochrosia elliptica* Labill.\(^4\) In the same year Woodward *et al.* assigned this plant alkaloid as 5,11-dimethyl-6H-pyrido[4,3-b]carbazole, confirmed by the first total synthesis.\(^5\) In the following years, ellipticine \(20\) and its analogues \(16-19\) (Figure 2) were isolated from various other species of the genera *Aspidosperma*, *Tabernaemontana*, *Strychnos*, and *Peschiera buchtieni*.\(^6\) In 1967, Australian scientists disclosed the antitumor activity of ellipticine and 9-methoxyellipticine toward various animal tumors.\(^7\) This discovery stimulated a strong interest in the synthesis of ellipticine and its analogues.

**Figure 2**
A derivative of 9-hydroxyellipticine, N-2-methyl-9-hydroxyellipticinium acetate 21 (elliptinium), was commercialized for clinical use in the treatment of myeloblastic leukemia, advanced breast cancer, and other solid tumors. In the late 1980s, a second generation of ellipticine-derived antitumor agents was developed, including the new clinical candidates datelliptium 22, retellipticine (BD-84) 23, and pazellipticine (PZE or BD-40) 24 (Figure 3). These findings initiated further extensive activities directed toward the synthesis of pyrido[4,3-b]carbazole derivatives for biological evaluation.

**Figure 3**

![Chemical structures of ellipticine derivatives](image)

The first total synthesis of ellipticine was reported by R. B. Woodward and co-workers in 1959. The bisindolyl derivative 26 of 3-acetylpyridine 25 upon reductive acetylation followed by pyrolysis at 200 °C provided ellipticine in just 2% yield (Eq. 1).
Cranwell and Saxton reported an efficient and simple synthesis of ellipticine from Indole 28 (Eq. 2). Indole was converted to 1,4-dimethylcarbazole 29. Vilsmeier-Haack formylation followed by condensation and cyclization with diethyl glycinal provided ellipticine in good yields.

**Eq. 2**

- **Pyranocarbazoles**
  
  Another important class of heteroarylcarbazoles is pyranocarbazoles. Many molecules with pyranocarbazole skeleton were isolated from nature. Girinimbine 37, the first member of the pyrano[3,2-a]carbazole alkaloids, was isolated from the stem bark of...
M. koenigii Spreng by Chakraborty et al.\textsuperscript{13} On the basis of chemical degradation studies, Chakraborty et al. proposed that the pyran ring and the aromatic methyl group are attached to different benzene rings of the carbazole nucleus.\textsuperscript{14} Later, Dutta and Quasim reassigned the structure of girinimbine on the basis of NMR studies and proposed that the pyran ring and the methyl group are at the same benzene ring.\textsuperscript{15} Chakraborty et al. also reported the isolation of murrayacine 38, a formyl analogue of girinimbine from two different natural sources, M. koenigii\textsuperscript{16} and C. heptaphylla.\textsuperscript{17} Furukawa et al. isolated in 1991 isolated the linear isomers, pyrayafoline B \textsuperscript{40} and E \textsuperscript{41}.\textsuperscript{19} In 1989, Reisch et al. isolated glycomaurin from Glycosmis mauritiana.\textsuperscript{20} In the following year, Furukawa et al. isolated the same compound from a different natural source, M. euchrestifolia Hayata, and named it eustifoline-A.\textsuperscript{21} Along with eustifoline-A 32, they also reported the isolation of the corresponding prenyl analogue, eustifoline-B 33.\textsuperscript{21}

Figure 4

Knöller and Gruner reported the synthesis of Girinimbine 37 by employing a palladium(II)-catalyzed one-pot triple C–H bond activation as key step leading to the Wacker oxidation with concomitant intramolecular oxidative C–C bond formation (Eq. \textsuperscript{3}).\textsuperscript{22} The diarylamine precursor is obtained by a palladium(0)-catalyzed Buchwald–Hartwig coupling of bromobenzene and aminochromene 42. The aminochromene 42 has been prepared in three steps and 70% overall yield starting from 2-methyl-5-nitrophenol.\textsuperscript{23}
Eq. 3

The Diels-Alder reaction between a quinone mono-imine and cyclic diene allows for the construction of substituted carbazoles in a regiospecific manner. This methodology has successfully been employed by M. A. Kerr and T. P. Lebold in a divergent strategy, culminating in the synthesis of eustifolines A-D and glycomaurrol.24

Readily available quinone imine 45 and diene 46 were converted to the tetrahydrocarbazole 47 via a Diels-Alder strategy followed by oxidative cleavage of the double bond (via the diol) followed by treatment of the resulting dicarbonyl with acid to afford the desired tetrahydrocarbazole in 61% yield over the four steps. Aldehyde reduction, tosyl removal, and dehydrogenation yielded carbazole 48 in 89% yield over the three steps. Tosyl removal was required to effect the dehydrogenation. Reduction of the aldehyde was found necessary to effect clean tosyl removal and dehydrogenation. The preparation of glycomaurrol as well as eustifolines D and A required reoxidation of 47 to the corresponding aldehyde (Eq. 4). Treatment with IBX in refluxing EtOAc afforded the desired aldehyde in excellent yield.25 Olefination of the crude aldehyde with a triphenylphosphonium isopropyl ylide followed by desilylation with TBAF yielded glycomaurrol in 86% yield. Cyclization of glycomaurrol 49 with PhSeCl followed by oxidation with H2O2 afforded eustifoline A 32 in 50% yield over the two steps.
Treatment of 47 with isopropenylmagnesium bromide followed by in situ generation of a ketene acetal en route to a Johnson-Claisen rearrangement led to the formation of ester 50 with the desired E geometry about the double bond in 86% overall yield (Eq. 5). Reduction to the aldehyde using DIBAL and olefination with triphenylphosphonium isopropyl ylide gave 51 bearing the requisite isopropylidene moiety in 78% overall yield. With the geranyl side chain installed, attention was turned to the dehydrogenative conversion of the tetrahydrocarbazole to the desired carbazole. N-Tosyl removal was effected with magnesium metal in methanolic aqueous ammonium chloride. The DDQ-mediated process which gave in 21% yield over the two steps. Desilylation gave eustifoline C 52 in 64% yield. Oxidative cyclization, using Pd(OAc)$_2$, generated eustifoline B 33 in 64% yield (Eq. 5).
• **Furocarbazoles**

In 1990, Ito and Furukawa isolated two new members of tetracyclic carbazole alkaloids, furostifoline 53 and the isomeric eustifoline D 54 from *M. euchrestifolia* Hayata (Figure 4).\(^{21}\) They were the first furocarbazole alkaloids obtained from natural sources. In the late 1990s, Wu *et al.* described the isolation and structural elucidation of two further furocarbazole alkaloids, furoclusaine A 55 and B 56 from the root bark of *C. excavata* (Figure 4).\(^{26}\)

**Figure 5**

![Furocarbazole structures](image)

In 1999, Timári *et al.* reported the total synthesis of furostifoline 53 from the bromocresol 57 (Eq. 6).\(^{27}\) The key steps of their approach are the Suzuki coupling to generate o-nitrobiaryl compound 61 and the subsequent reductive cyclization via a nitrile intermediate. Annulation of the furan ring at the bromocresol 57 by reaction with bromoacetaldehyde diethyl acetal afforded 5-bromo-7-methylbenzofuran 59. A halogen/metal exchange reaction of 5-bromo-7-methylbenzofuran 59 with n-butyllithium and subsequent treatment with tributyl borate gave the boronic acid derivative 60. The palladium(0)-catalyzed cross-coupling of the boronic acid derivative 60 with 2-bromonitrobenzene provided the o-nitrobiaryl compound 61 in 72% yield. Using Cadogan’s method, by reductive cyclization with triethyl phosphite,\(^{28}\) the o-nitrobiaryl compound 61 was transformed to furostifoline 53 in 42% yield (Eq. 6). Thus, furostifoline 53 was made available in five steps and 10% overall yield based on compound 57.
Eustifoline D 54 was prepared by oxidizing carbazole 48 and subjecting the resulting aldehyde to desilylation with TBAF followed by treatment with acid to effect benzofuran formation in 53% yield over the three steps (Eq. 8).\textsuperscript{24}

Hibino and co-workers described the total synthesis of furostifoline 53 from 2-chloro-3-formylindole 62 using the electrocyclic reaction of an intermediate allene with the 2,3-double bonds of indole and furan as the key step (Eq. 7). Suzuki cross-coupling of 2-chloro-3-formylindole 62 and furan-3-boronic acid,\textsuperscript{29} protection as the benzyloxymethyl (BOM) ether, Grignard reaction of the N-BOM-protected 2-(fur-3-yl)indole-3-carbaldehyde with ethynylmagnesium bromide, and again BOM-protection of the propargylic alcohol provided in four steps the 2-(fur-3-yl)-3-propargylindole 63. Using thermal reaction conditions the 2-(fur-3-yl)-3-propargylindole 63 was transformed to the 4-oxygenated furo[3,2-a]carbazole. Deprotection of compound under Birch conditions led to furo[3,2-a]carbazole 64 (51%). For the final transformation of the furocarbazole 64 to furostifoline 53, the hydroxy group was removed via reductive elimination\textsuperscript{30} of the intermediate triflate (Eq. 7).\textsuperscript{31} This route affords furostifoline in nine steps and 43% overall yield.
Introduction

Eq. 8

- Carbazolocarbazoles

Carbazolocarbazoles constitute another versatile class of heteroarylcarbazoles. These are the molecules with one carbazole attached with another carbazole skeleton at various positions. To the carbazolocarbazole family belong the five different isomeric ring systems namely carbazolo[2,3-a]carbazole 65, carbazolo[2,3-b]carbazole 66, carbazolo[2,3-c]carbazole 67, carbazolo[3,2-a]carbazole 68 and carbazolo[3,2-b]carbazole 69 (Figure 5). Among these, the most interesting structural class is the carbazolo[2,3-a]carbazoles 65. The carbazolo[2,3-a]carbazole framework 65 is found in many natural products with a broad range of potent biological activities, e.g. antifungal, antimicrobial, antitumor, and antihypertensive activity. Their activity as potent inhibitors of protein kinase C (PKC) has received special attention and was the focus of several investigations. The carbazolo[2,3-b]carbazole 66, carbazolo[2,3-c]carbazole 67, carbazolo[3,2-a]carbazole 68, carbazolo- [3,2-b]carbazole 69 and their derivatives have been studied in much less detail. This is explained by the fact that they are not present in natural products and there is a lack of knowledge of their biological activities. The diverse synthetic approaches to the isomeric carbazolocarbazole ring systems 65-69 were summarized in chapter 4.
Introduction

Bringmann et al. reported a biomimetic oxidative dimerization of the monomer\textsuperscript{35,36} 72 with di-\textit{tert}-butyl peroxide (t-BuO)\textsubscript{2} afforded the 2,2′-linked bis(O-demethylmurrayafoline-A) 73 in 81% yield.\textsuperscript{37}

Eq. 9

Knölliker and co-workers described the first total synthesis of 1,1′-bis(2-hydroxy-3-methylcarbazole) 75 via molybdenum-mediated construction of the carbazole framework.\textsuperscript{38} The required monomer, 2-hydroxy-3-methylcarbazole 74, was obtained in three steps and 22% overall yield starting from dicarboxyl(4-cyclohexa-1,3-diene)(5-cyclopentadienyl)molybdenum hexafluorophosphate\textsuperscript{39} and 3-methoxy-4-methylaniline as synthetic precursors. Oxidative coupling of the monomer 74 using
*Electrophilic cyclization*

Alkynes are versatile building blocks in organic synthesis. A wide range of carbocycles and heterocycles have been prepared by the electrophilic cyclization of functionally substituted alkynes\(^ {41}\) and by transition metal-catalyzed annulations.\(^ {42}\) Recently, Larock and others have reported that the electrophilic cyclization of alkynes can be a very powerful tool for the preparation of a wide variety of interesting carbocyclic and heterocyclic compounds, including benzofurans,\(^ {43}\) furans,\(^ {44}\) benzothiophenes,\(^ {45}\) thiophenes,\(^ {46}\) benzopyrans,\(^ {47}\) benzoselenophenes,\(^ {48}\) selenophenes,\(^ {49}\) naphthols,\(^ {50}\) indoles,\(^ {51}\) quinolines,\(^ {52}\) isoquinolines,\(^ {53}\) R-pyrones,\(^ {54}\) isocoumarins,\(^ {54}\) isochromenes,\(^ {55}\) isoindolinones,\(^ {56}\) naphthalenes\(^ {57}\) and polycyclic aromatics,\(^ {58}\) isoxazoles,\(^ {59}\) chromones,\(^ {60}\) bicyclic-lactams,\(^ {61}\) cyclic carbonates,\(^ {62}\) pyrroles,\(^ {63}\) furopyridines,\(^ {64}\) spiro[4.5]trienones,\(^ {65}\) coumestrol and coumestans,\(^ {66}\) furanones,\(^ {67}\) benzothiazine-1,1-dioxides,\(^ {68}\) etc.\(^ {69}\) In general, these electrophilic cyclization reactions are very efficient, afford clean reactions, proceed under very mild reaction conditions in short reaction times, and tolerate almost all important functional groups. Furthermore, the iodine-containing products can be further elaborated to a wide range of functionally substituted derivatives using subsequent palladium-catalyzed processes. These reactions are generally believed to proceed by a stepwise mechanism involving electrophilic activation of the alkyne carbon-carbon triple bond, intramolecular nucleophilic attack on the cationic intermediate and subsequent de-alkylation.

This electrophilic cyclization methodology has been applied to a variety of unsymmetrical functionally substituted diarylalkynes and the resulting products characterized in order to determine the relative reactivities of various functional groups toward electrophilic cyclization. The required diarylalkynes are readily
prepared by consecutive Sonogashira reactions\textsuperscript{70} of appropriately substituted aryl halides. Thus, Sonogashira substitution with trimethylsilyl acetylene, removal of the TMS group, followed by a second Sonogashira reaction, generally affords moderate to excellent yields of the desired diarylalkynes. A number of factors affect the cyclization. These include electronic (relative nucleophilicity of the functional groups, polarization of the carbon-carbon triple bond, and the cationic nature of the intermediate) and steric factors (hindrance and geometrical alignment of the functional groups), as well as the nature of the electrophile.

Three kinds of results have been observed for these competitive cyclizations. (1) Only one of the two possible products has been obtained. This is most common, indicating that there is a hierarchy of functional group reactivity toward the electrophilic cyclizations. Assuming that the various factors mentioned above may affect the cyclization, the dominance of one functional group over another can be attributed to any one or a combination of two or more factors operating in favor of the one functional group over the other. (2) A mixture of both possible products has been observed. This occurs less commonly, but even in these cases, one product is often obtained in a significantly higher yield than the other, indicating that one group is usually significantly more reactive toward cyclization. (3) A complex reaction mixture is obtained. Although this does not provide any substantial information about the relative reactivity, it points to the fact that either the more reactive functional group is not compatible with the particular reaction conditions or neither of the two functional groups involved has a dominant reactivity, thus resulting in a complex reaction mixture. It also should be noted that since these reactions are very fast in general, and may involve multiple steps and intermediates, it is quite difficult to strictly assign the reactivity of any particular functional group to any one factor mentioned above. Indeed in some cases one or more factors are operating in opposition to each other, resulting in a mixture of products.

Jie Wu \textit{et al} reported a highly efficient silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and α,β-unsaturated carbonyl compound which affords H-pyrazolo[5,1-a]isoquinoline-1-carboxylates in good yield (Eq. 11).\textsuperscript{71} They explained that after condensation of 2-alkynylbenzaldehyde \textsuperscript{76} with sulfonohydrazide, \(N\)'-(2-alkynylbenzylidene)hydrazide would be obtained. In the presence of AgOTf, the triple bond would be activated and then the 6-\textit{endo}-cyclization occurred to afford the isoquinolinium-2-yl amide. Subsequently, acrylate \textsuperscript{77} would be involved in the [3+2] cycloaddition process to generate the intermediate. After
release of tosyl group and aromatization, *H*-pyrazolo[5,1-*a*]isoquinoline-1-carboxylate 78 was then afforded.

**Eq. 11**

Jim Li and coworkers described a one-pot synthesis of phthalides via an intramolecular 5-exo-dig cyclization of ortho-alkynylbenzaldehydes under mild NaClO₂ oxidation conditions.²² The alkynylaldehyde 79 was oxidized to acid 80, which further cyclizes by the activation of triple bond to the products 81 and 82 (Eq. 12).

**Eq. 12**

Waldmann *et al.* reported silver catalyzed and microwave assisted one-pot cascade synthesis which provides efficient access to diverse alkaloid-inspired scaffold classes (Eq. 13) and a concise and efficient total synthesis of homofascaplysin C and fascaplysin.⁷³

**Eq. 13**

*Boc*-protected 3-ethynyl-indole-2-carbaldehyde 85 was employed as a common precursor for the natural product targets fascaplysin 91 and homofascaplysin C 88. The microwave assisted silver catalyzed cascade cyclization of 85 with aniline 86 yielded the pentacyclic core 87 in high yield after acidic work-up. Partial reduction of the tert-butyl ester (60% conversion) by means of *in situ* generated lithium
diisobutylpiperidinohydroaluminate provided the natural product homofascaplysin C \(88\) in 48% overall yield over four steps from \(85\) (Eq. 14). To overcome the difficult reduction of the tert-butyl ester \(87\) to final product \(88\), aniline \(89\) was employed in the cascade synthesis of pentacyclic core \(90\) which was obtained in 61% yield. Formylation of \(90\) with POCl\(_3\) cleanly provided homofascaplysin C \(88\) with an overall yield of 53%. In addition, the pentacyclic core \(90\) was efficiently transformed to the natural product fascaplysin \(91\) by oxidation with peracetic acid, followed by salt formation in 52% overall yield (Eq. 14).\(^74\)

\[\text{Eq. 14}\]

\[
\begin{align*}
\text{NH}_2\text{CO}_2\text{tBu} \quad & \text{NH}_2\text{CO}_2\text{tBu} \\
\text{86} & \quad \text{89} \\
\text{N} & \quad \text{N} \\
\text{85} & \quad \text{Boc} \\
\text{88} & \quad \text{Homofascaplysin C} \\
\text{87} & \quad \text{88} \\
\text{i}) \quad n\text{-BuLi, DIBAH} & \quad \text{ii}) \quad 1N \text{ HCl} \\
\text{DMF, POCl}_3 & \quad \\
\text{N} & \quad \text{N} \\
\text{90} & \quad \text{91} \\
\text{i}) \quad \text{CH}_3\text{CO}_2\text{H, MeOH, AcOH} & \quad \text{ii}) \quad \text{Conc. HCl} \\
\text{Fascaplysin} & \quad \text{Cl}^{-} \\
\end{align*}
\]

J.-H. Li and co-workers have developed an efficient tandem route to the synthesis of iodoisoquinoline-fused benzimidazole derivatives including an iodocyclization strategy (Eq. 15).\(^75\) In the presence of CuI, a variety of 2-ethynylbenzaldehydes \(75\) underwent the tandem reaction with benzenediamines \(92\) and iodine to afford the corresponding iodoisoquinoline-fused benzimidazoles \(94\) and bromoisooquinoline fused benzimidazoles \(93\) in moderate to good yields.

\[\text{Eq. 15}\]

\[
\begin{align*}
\text{93} & \quad \text{94} \\
\text{92} & \quad \text{93} \\
\text{NBS, CuI} & \quad \text{DMSO, 120 °C} \\
\text{75} & \quad \text{92} \\
\text{R} & \quad \text{R} \\
\text{I} & \quad \text{Br} \\
\end{align*}
\]
Y. Yamamoto et al. reported the reaction of o-alkynyl(oxo)benzenes 95 with alkynes 96 in the presence of a catalytic amount of AuCl₃ in (CH₂Cl)₂ at 80 °C which gave the [4+2] benzannulation products, naphthyl ketone derivatives 98 and 99 in high yields (Eq. 16). When the reaction was carried out using AuBr₃ instead of AuCl₃, the reaction speed was enhanced and the chemical yield was increased. On the other hand, when the reaction was carried out in the presence of a catalytic amount of Cu(OTf)₂ and 1 equiv. of a Bronsted acid, such as CF₃CO₂H, in (CH₂Cl)₂ at 100 °C, the decarbonylated naphthalene products 97 were obtained in high yields.

Eq. 16

**Tandem Reactions**

The future of organic synthesis lies in efficient methodology and the discovery of new processes for building up complex chemical architecture using simple techniques. Brevity in organic synthesis is of paramount importance for industry and over the past few years there were dramatic improvements in this subject and the development of novel catalysts for achieving tandem reactions. Such processes will minimize waste and costs will be kept to a minimum thus increasing efficiency. Transition metal catalyzed tandem reactions have emerged as a useful tool for the synthesis of multiring heterocyclic compounds because of the intriguing selectivity, atom economy, and exceptional ability to activate n systems, especially alkynes, towards intermolecular and intramolecular nucleophilic attack. Among the transition-metal-catalyzed reactions, palladium is extensively used because of its tolerance of many functional groups and its low toxicity. However, in recent years copper-catalyzed reactions have received considerable attention because of their efficiency and low costs. The reported annihilation chemistry for the synthesis of heterocycles from alkynes proceeds through n complexation of the alkyne and subsequent attack of the resulting metal complex onto the appropriate adjacent functionalized arene. Metal-free approach to tandem reactions attracts the chemists due to economical and environmental factors.

Fu et al. have developed a simple and efficient copper-catalyzed one-pot tandem method for synthesis of benzimidazo[1,2-b]isoquinolin-11-one derivatives
via reactions of substituted 2-halo-N-(2-halophenyl)benzamides 100 with alkyl 2-cyanoacetates 101 or malononitrile under mild conditions (Eq. 17).  

**Eq. 17**

A facile and direct synthesis of diversely-substituted, medicinally-useful indolo- and pyrrolo[2,1-a]isoquinolines 106 in good yields with excellent regioselectivity was reported by A. K. Verma and co-workers (Eq. 18).  

**Eq. 18**

Che and Liu have described a new, efficient platinum(II) catalyzed tandem cyclization reaction from simple, readily available starting materials to furnish multiply substituted indolines 109 in excellent yields with high regioselectivity under mild reaction conditions (Eq. 19). The procedure is easy to perform and allows for a straightforward, diversity-oriented and regioselective synthesis of indoline derivatives with a broad substrate scope, thus rendering the method a valuable addition to alternative indoline syntheses.

**Eq. 19**
- **Metal-free tandem reactions**

A copper-free tandem strategy using easily obtained β-ketoarylaldehydes 110 and amines 111 as starting material for the synthesis of 3-substituted 4-quinolones 112 is reported by Zhu *et al* (Eq. 20). The strategy gives 3-substituted quinolones 112 in up to 97.5% yield without isolation of intermediates, and is tolerant of a wide range of functional groups and applicable to library synthesis.85

**Eq. 20**

```
\[
\begin{align*}
\text{R}_1 & \text{Br}\text{R}_2 & + & \text{R}_3\text{NH}_2 \\
\text{110} & & & \text{111} \\
\rightarrow & \text{DMSO, 100 °C, K}_2\text{CO}_3, 130 °C \rightarrow & \text{R}_1 & \text{R}_2 & \text{N}\text{R}_3 \\
\text{112} & & & & \\
\end{align*}
\]
```

Liu and co-workers have developed86 a mild and effective method for the construction of 3-hydroxyisoindolin-1-ones 115 via a metal-free tandem transformation using a phase transfer catalyst in good yields with excellent regioselectivity (Eq. 21). Significantly, the strategy presents an atom-economical and environmentally friendly transformation, and has a high functional group tolerance.

**Eq. 21**

```
\[
\begin{align*}
\text{R}_3 & \text{OH} & \rightarrow & \text{NH}_2 \\
\text{R}_1 & \text{R}_2 & \text{113} & \rightarrow & \text{Bu}_4\text{NOAc} & \text{H}_2\text{O / M.W} \\
\rightarrow & \text{R}_1 & \text{R}_2 & \text{N}\text{R}_3 & \text{115} \\
\end{align*}
\]
```

Wang and Liu reported a facile multi-component synthesis of highly substituted phenols 119 has been developed starting from readily available acyclic precursors under mild conditions (Eq. 21).87 In the first stage, the [4 + 1 + 1] annulation of an aldehyde 117 and two different methyl ketones 116 and 118 involving an aldol condensation/intermolecular Michael addition/intramolecular Michael addition/elimination of ethanethiol sequence, is highly chemo and regioselective since the two ketones show different reactivities.
\textbf{Iodocyclization}

The iodocyclization of alkynes has emerged as an efficient tool for the synthesis of important heterocycles and carbocycles. In general, iodocyclization is a very efficient reaction, proceeds under very mild reaction conditions and exhibits a very broad scope in terms of the functional group/substituent compatibility.\textsuperscript{88} As iodine is known to be an excellent handle for further elaboration through transition-metal catalyzed cross-couplings, especially palladium-catalyzed transformations,\textsuperscript{89} the iodocyclization products are ideal substrates for further functionalization and a rapid increase in molecular diversity. Polyheterocyclic compounds (PHCs) of this type have found applications in biological as well as materials chemistry.\textsuperscript{90,91} The general strategies employed for poly-heterocycle synthesis involves the Sonogashira coupling of a functionally substituted haloarene with a functionalized alkyne. The alkyne is then subjected to iodocyclization, and the resulting 3-iodoheterocycle is generally isolated in good to excellent yields. The resulting iodine-containing heterocycle can be used as the starting material for further iterative cycles of Sonogashira coupling and iodocyclization to generate the desired polyheterocyclic molecule.

In recent years, molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available reagent to effect iodocyclization and cyclodehydroiodination reactions of tethered heteroatom-containing alkenyl or alkynyl systems to afford heterocyclic compounds with many synthetic and biological applications. Although halogen molecules on their own are nonpolar, they are easily polarized by the $n$ electrons of the C-C multiple bond to become electrophilic. The electrophilic properties of iodine have been exploited over the years to effect cyclization of heteroatom-containing alkenyl and alkynyl derivatives. Halocyclization is a reaction whereby the intramolecular nucleophilic group attacks the carbon–carbon double or triple bond activated by electrophilic halogenating reagent to give cyclic compounds (Eq. 23). The outcome of this cyclization strategy is rationalized in terms of the rules previously developed by Baldwin for predicting the relative ease of organic ring-forming reactions. The physical bases for these three rules are the
stereochemistry requirements of the transition states for various tetrahedral, trigonal, and digonal systems in nucleophilic, homolytic, and cationic ring closure processes. Iodocyclization of tethered heteroatom-containing alkenyl or alkynyl derivatives as well as iodocyclization of 2-allyl-1,3-dicarbonyl derivatives take advantage of the electrophilic nature of iodine.

Eq. 23

\[
\text{LG} = \text{Leaving Group} \\
X = O, S, NMe \text{ etc} \\
R = \text{Alkyl, Aryl, Vinylic, TMS}
\]

Larock et al. reported a simple strategy for the synthesis of polyheterocyclic compounds. After successful implementation of this general strategy for the efficient synthesis of PHCs, several variations in the approach have been explored that further highlight the versatility and scope of this methodology. First, iodocyclization can be carried out quite selectively affording a variety of intermediates, which should prove quite versatile for further elaboration. A variety of heterocyclic units are readily accessible by this iodocyclization strategy. This approach can be combined with other efficient transformations to broaden the scope of the methodology and allow easy access to heterocycles that are not presently accessible by iodocyclization. For example, in an effort to synthesize fused polyheterocyclic compounds, the benzothiophene derivative 122 was subjected to silyl-iodine exchange (Eq. 24). The resulting 2,3-diodobenzothiophene 123 on double Sonogashira coupling with an appropriate \( \sigma \)-functionalized terminal alkyne 124, followed by double cyclization, quickly leads to a compound 125, having three linked heterocyclic units and two iodine handles. The diodo compound 125 was then subjected to a palladium-catalyzed Ullmann reaction leading to the formation of fused heterocycle 126 (Eq. 24). Similar fused heterocyclic systems have been shown to exhibit interesting electronic and luminescent properties. This approach can be conveniently extended to the synthesis of symmetrical fused heterocycles as well. PHCs such as these should prove useful as ligands in coordination and organometallic chemistry.
Eq. 24

Plicadin 132 was synthesized by Laroc and co-workers employing iodocyclization methodology (Eq. 25). Hydrolysis of the known chromene carbamate 127,95 followed by protection of the resulting OH group as an acetoxy group, afforded chromene 128 in a 51% overall yield (Eq. 25). Sonogashira coupling of 128 with 129 under our previous optimized conditions led to alkyne 130 in a moderate yield. Iodocyclization of 130 afforded 3-iodobenzofuran 131 in a good yield (Eq. 25). Under optimal conditions for the Pd-catalyzed lactonization, benzofuran 131 is converted to the proposed plicadin tosylate in a 61% yield, which was nearly quantitatively converted to plicadin 132 by deprotection with TBAF.

Eq. 25
• **Solvent-free reactions**

Chemists still carry out their reactions in solution, even when a special reason for the use of solvent cannot be found. Many reactions proceed efficiently in the solid state.\(^{96}\) Indeed, in many cases, solid-state organic reaction occurs more efficiently and more selectively than does its solution counterpart, since molecules in a crystal are arranged tightly and regularly. Furthermore, the solid-state reaction (or solvent-free reaction) has many advantages: reduced pollution, low costs, and simplicity in process and handling. Solvent-free thermal reactions are important for practical synthetic processes in industry. The occurrence of efficient solid-state reactions shows that the molecules reacting are able to move freely in the solid state.

A new and simple modification of the Biginelli dihydropyrimidinones 136 from aldehydes 133, urea 134 and 1,3-dicarbonyls 135 by using Yb(OTf)\(_3\) as a catalyst and under solvent-free reaction conditions was reported by Quin and co-workers (Eq. 26).\(^{97}\)

**Eq. 26**

![Equation 26](image)

As reported by Desiraju and co-workers,\(^{98}\) several substituted 2'-hydroxy-4',6'-dimethylchalcones 137 undergo a solid-state intramolecular Michael-type addition reaction to yield the corresponding flavanones 138, at temperatures below their melting points. Conversions of the chalcones 137 to flavanones 138 could be followed by the orange to pale yellow color change (Eq. 27). X-ray studies of the reactant and product indicate that these reactions proceed in a non-topochemical fashion.

**Eq. 27**

![Equation 27](image)

However, not all organic synthesis can be carried out in the absence of solvent. Some organic reactions proceed explosively in the solid state. In such cases, solvent is useful in order to mediate the reaction rate. Finally, it is always important
to choose the best conditions for organic synthesis. For reactions that proceed moderately in the absence of solvent or in a water suspension, then solid-state reaction would be the better choice. For reactions that proceed vigorously in the solid state, then solution reaction in a nontoxic solvent would be better.

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Introduction


